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ON THE EXISTENCE OF AN INTRINSIC DEFICIENCY IN PELLAGRA.

A PRELIMINARY REPORT.

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FOR a number of years there has been doubt of the total validity of Goldberger's theory that pellagra is entirely a manifestation of nutritional deficiency. McLester[1] has pointed out some of the objections to this hypothesis. It has been the experience of many that severe advanced cases are poorly controlled by diet and vitamin therapy. Of 440 cases of pellagra observed in this clinic during the 15-year period, 1919 to 1934, 119 (27.02%) died. The mortality rate, during the years 1924 to 1934, when yeast was used lavishly to fortify the diet, was 25.5% which compared favorably with the rate of 37.5% which prevailed before that time, but was still discouragingly high. Several observers, including Spies[2,3] and the authors, have seen remission or recovery while patients were on pellagra-producing diets. It is well known that chronic alcoholism and extensive neoplastic or obstructive lesions of the stomach may

be associated with the development of pellagra. Occasionally the disease has been seen to occur in individuals seemingly adequately nourished in all respects and free from alcoholism or obstructive disease of the gastro-intestinal tube. Since the discovery of the relation of liver extracts and desiccated stomach to recovery in pernicious anemia, Spies,[4,6,7] Ruffin and Smith,[5] and others have drawn analogies between this disease and pellagra and have had success in treating pellagra with liver and stomach preparations. Improvement in patients so treated has been attributed to a protective influence exercised by stomach on vitamin B_2 or to the high B_2 content of liver extracts, but Spies[3] suggested a secondary factor analogous to the gastric deficiency in pernicious anemia.

Pellagrins clinically may be separated into three general groups: The mild, who recover spontaneously on diets nutritionally inadequate but fairly high in calories; the severe, who mend slowly on a diet high in caloric value enriched with vitamins; and the intractable, who are prone to die febrile or demented in spite of all remedial measures. Admitting that an extrinsic deficiency is active in the production of pellagra and that the essential substance is in all likelihood the B_2 complex; and not denying that factors as diverse as infection, seasonal influences and excessive solar radiation may play a part in the genesis of the disease, an explanation is necessary for the fact that many patients fail to improve when the essential substance is administered even in great excess. If it could be shown that an intrinsic factor exists which is necessary for the utilization of the extrinsic factor B_2, many of the paradoxes of pellagra might be explained. It might be inferred that prolonged deficient intake of extrinsic factor leads to exhaustion or failure of production of intrinsic factor in certain individuals with development of the symptom complex of pellagra. In some, sufficient intrinsic factor may remain or be regenerated to make possible utilization of minimal amounts of extrinsic factor. In others, a large intake of extrinsic factor may promote rapid regeneration of intrinsic. In others still, intrinsic factor is lacking and cannot regenerate even in the presence of abundant extrinsic factor which, therefore, is not utilized.

In imitation of the work of Castle and his associates[8–12] on pernicious anemia it was determined to test the efficacy of normal gastric juice as a source of an hypothetical intrinsic factor. The patients to whom gastric juice was given were typical advanced cases of pellagra. Recent alcoholism and obstructive lesions of the gastro-intestinal tract were absent.

Method. Five patients were maintained on the original Goldberger-Wheeler pellagra-producing diet to which was added 25 gm. of fat salt pork. As eaten, the diet had a daily caloric value approximating 1400 C. and contained approximately 260 gm. of carbohydrate, 25 gm. of protein

and 30 gm. of fat. Sources of B_2 were minimal, collards being the only article of diet containing it in appreciable quantities. One patient was desperately ill and stuporous and was given the routine liquid pellagra diet used in treatment of the most severe cases. In the absence of any quantitative method of estimating improvement or regression impressions were based on the mental state, progress or resolution of dermatitis, glossitis and stomatitis, frequency of stools and gain in weight. Three patients were held on the pellagra-producing diet for a preliminary observation period of 2 weeks or more. One patient was given during the observation period amounts of hydrochloric acid comparable to the normal daily secretion. As items of interest weekly analyses of gastric juice obtained after histamin were recorded and tongue prints were made at weekly intervals. It is not to be inferred that any relation is implied between the degree of gastric acidity and the presence of intrinsic factor. Gastric juice was obtained from normal medical students and from patients with no gastrointestinal disease. To obviate the probability of increased gastric digestion of food, all doses of gastric juice were administered in the evening some 4 hours after the evening meal.

Case Abstracts. Case 1. (No. 92931.) B. R., female negro, aged 45, was admitted, October 25, 1934, with symptoms of 4 months' duration. She was emaciated, weighed 75 pounds and had a typical pellagrous dermatitis of forehead, face, hands, forearms and feet. The tongue was bright red with advanced papillary atrophy; there was moderate stomatitis. Diarrhea with 4 to 5 stools daily had been present for 1 month. Temperature, 99° F.; pulse, 110; respiration, 24; blood pressure, 96/74. General physical examination was not remarkable. The urine was negative. The blood contained hemoglobin, 80%; R.B.C., 3,930,000; W.B.C., 8300. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were positive. Analyses of gastric contents are tabulated below.

Table 1.—Analyses of Gastric Contents.

Date.	Free HCl.	Total acidity.
1934.		
Oct. 25	0	5
Nov. 17	0	8
29	0	8
Dec. 6	44	60
12	39	54
24	20	42
31	15	35
1935.		
Jan. 26	40	58

This patient was fed the regular ward diet for 22 days, during which she became slightly worse, with increasing stomatitis and diarrhea. Her weight on November 17 was 75½ pounds, when she was put on pellagra-producing diet. During the ensuing 2 weeks there was definite increase in dermatitis and stomatitis, diarrhea, with 5 or 6 stools daily, persisted. On November 29, her weight was 75½ pounds. On this day and the 9 ensuing days she was given 200 gm. of ground raw lean beef incubated with 200 cc. of normal gastric juice, according to Castle's technique,[10] which was administered at 8 P.M. by stomach tube. On December 2, marked improvement in the stomatitis and glossitis was noted. On December 6, stomatitis was healed, the tongue had lost its glossy redness, there was beginning desquamation of the skin lesions, and diarrhea had lessened to 2 stools daily. Subjective improvement was marked and the weight was 78 pounds. On December 9, after 10 doses of beef incubated in gastric juice, treatment was discontinued. Clinical improvement was remarkable,

the mouth looked normal, the tongue was pink and showed regeneration of papillæ. The skin lesions were far advanced in resolution and stools reduced to 1 daily. It was decided to maintain this patient on pellagra-producing diet and to expose her to direct sunlight in an effort to produce a relapse. She continued to show clinical improvement with complete resolution of skin lesions, absence of diarrhea and subjective well-being. On December 24, the weight was 83 pounds; on January 6, 1935, she was dismissed, clinically cured, weighing 88 pounds. She was observed on January 26, when gastric contents were secured, and at intervals until September 1, 1935. There has been no recurrence of pellagra.

COMMENT. This patient, after administration of 200 gm. of raw beef incubated with 200 cc. of normal gastric juice daily for 10 days, showed extraordinary improvement which was maintained during a subsequent observation period of 4 weeks, during which she remained on pellagra-producing diet and was frequently exposed to sunlight. Eight months later no signs of pellagra could be detected. It is felt that this woman cannot be said to have improved as a result of gastric juice alone; the lean beef used is considered an excellent source of B_2. The rather spectacular remission may have been due to administration of large amounts of both extrinsic and intrinsic factor. On this account no similar experiment was carried out.

CASE 2.—(No. 93433.) H. S., aged 33, a white male, was admitted, November 11, 1934, with symptoms of 4 months' duration. He was fairly well nourished; weighed 131 pounds. Typical pellagrous dermatitis of malar eminences, hands, forearms and feet. The tongue was smooth, bright red and fissured; there was no marked stomatitis. Diarrhea had been present for 6 weeks, averaging 5 stools daily. Mild dementia was present. Temperature, 100° F.; pulse, 88; respiration, 20. General physical examination showed nothing unusual. The urine was negative. The stools contained no parasites. The blood contained hemoglobin, 80%; R.B.C., 4,580,000; W.B.C., 6700. The Wassermann and Kahn tests were positive. Routine blood chemical determinations were normal. The results of analyses of gastric contents are tabulated below.

TABLE 2.—ANALYSES OF GASTRIC CONTENTS.

Date. 1934.	Free HCl	Total acidity
Nov. 12	0	8
25	0	7
Dec. 1	0	14
8	32	43

This man was put on pellagra-producing diet for 2 weeks, at the end of which dermatitis and glossitis were worse; diarrhea was somewhat less, averaging 4 stools daily. The mental state was distinctly worse; he was morose, irritable and inclined to be uncoöperative. From November 25 to December 4, inclusive, normal gastric juice in amounts varying from 150 to 300 cc. was given daily at 8 P.M. On December 1, definite improvement could be noted; the tongue was pink and showed slight regeneration of papillæ; the skin lesions were desquamating, leaving smooth red surfaces. The stools were reduced to 2 daily. Pellagra-producing diet was continued until his dismissal from the hospital, on December 13. At this time he was clinically well. The tongue looked normal, the areas of dermatitis had

completely desquamated, stools were 1 daily and the mental state seemed normal. The weight was 133 pounds.

CASE 3.—(No. 93485.) R. M., a white female, aged 58, was admitted, November 21, 1934, with symptoms of 3 weeks' duration and sudden onset, on November 1, with diarrhea and soreness of the mouth and tongue. Eruption appeared on the hands about November 15. She had been under observation and treatment in the Out-Patient Department since November 5. She was fairly well nourished; weight, 128 pounds. There was edema and bright red erythema of the forehead, bridge of the nose, hands, wrists and forearms. The tongue was bright red, ulcerated at the edges, slightly atrophic; there was moderate stomatitis. General physical examination revealed nothing significant. The temperature was 100° F.; pulse, 88; respiration, 20. The urine contained traces of albumin. The stools contained no parasites. The blood contained hemoglobin, 70%; R.B.C., 3,600,000; W.B.C., 8750. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were negative. Results of analyses of gastric contents are tabulated below.

TABLE 3.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1934.		
Nov. 22	0	7
28	28	36
Dec. 5	20	22
12	12	27
1935.		
Oct. 3	5	17

Since this woman was acutely ill with slight fever, a rapidly developing eruption and severe diarrhea averaging 9 stools daily it was not thought wise or necessary to hold her for an observation period. She was given the pellagra-producing diet, and normal gastric juice in amounts varying from 160 to 270 cc. were given daily from November 22 to December 1, inclusive. On November 24, definite recession of dermatitis and stomatitis was noted and the stools were reduced from 9 to 3 in 24 hours. On December 1, dermatitis had resolved, leaving slight reddening of the skin, and stomatitis and glossitis had disappeared. Stools were 1 daily. She was subjectively well. She was kept on pellagra-producing diet during the remainder of her stay in the hospital and discharged, December 13, clinically well. She has been followed up to the present time and has had no relapse.

CASE 4.—(No. 93928.) J. H., a negress, aged 23, was admitted, December 13, 1934. There had been 3 previous admissions to the hospital, on March 16, 1931, July 9, 1931 and May 4, 1932. On each occasion the diagnoses were pellagra and sicklemia. The present relapse began 4 weeks before admission, with diarrhea up to 6 stools daily; stomatitis and dermatitis appeared 3 weeks before admission. She was emaciated; weight, 71½ pounds. The forehead, nose, cheeks and chin presented the "pellagrous mask." There was severe moist dermatitis of the hands, wrists and forearms, dry dermatitis of elbows, feet and ankles. There was vaginitis thought to be of pellagrous origin. There was severe stomatitis, the tongue was atrophic but not red or ulcerated. There was slight mental confusion. General physical examination showed no other gross abnormalities. The temperature was 99° F.; pulse, 92; respiration, 20. The urine was concentrated and contained a few leukocytes. The stools contained no parasites. The blood contained hemoglobin, 30%; R.B.C., 1,650,000; W.B.C., 9000. Sicklemia was present. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were negative. Results of analyses of gastric contents are tabulated below.

This patient was put on pellagra-producing diet with no preliminary observation period. It was decided to give hydrochloric acid in amounts theoretically equivalent to normal daily secretion: 100 cc. of 2.92% HCl were diluted to 300 cc. and given through a stomach tube each night at 8 P.M. This was the amount of acid calculated to be present in 1500 cc. of gastric juice at an acidity of 50° C. free HCl. No discomfort was occasioned by this dosage. The patient's condition grew gradually worse with increasing stomatitis, dermatitis, diarrhea up to 7 stools daily and increasing mental confusion. On January 4, 1935, her condition was alarming after 3 weeks of acid therapy, and acid was discontinued. On this day, and for 11 subsequent days, she was given gastric juice in amounts varying from 180 to 300 cc. daily at 8 P.M. By January 8, her stomatitis was much improved, diarrhea reduced to 2 stools daily and the moist dermatitis was drying. On January 13, she developed an acute upper respiratory infection which caused fever for 17 days. In spite of this her pellagrous manifestations improved rapidly, so that on January 16, the day after treatment with gastric juice was discontinued, it was noted that stomatitis was healed, dermatitis desquamating and diarrhea absent. The mental state was much improved. From this time improvement was gradual, with slow resolution of dermatitis and improvement in the mental condition. The patient was hospitalized until March 13, constantly on pellagra-producing diet, in an effort to provoke an early relapse. At the time of discharge all pellagrous manifestations had been absent for 1 month and weight had increased to 89 pounds. The hemoglobin was 50%; R.B.C. 2,300,000; W.B.C., 6250.

TABLE 4.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1934.		
Dec. 18	0	8
24	0	3
1935.		
Jan. 1	0	5
9	0	5
16	0	5
21	0	7
Feb. 2	0	7

Weekly examinations, from February 9 to date of discharge, showed no change in the gastric contents.

CASE 5.—(No. 97426.) V. D., a negress, aged 38, was admitted, June 15, 1935. No history was ever obtainable. She was emaciated, weighing 76 pounds, and was comatose, with extensive dermatitis of the hands, wrists, forearms, elbows and feet. A vaginitis was thought to be of pellagrous origin. There was ulcerative stomatitis with salivation and marked glossitis with atrophy of the papillæ. General physical examination showed no gross abnormalities other than evidences of extreme dehydration. The urine was concentrated, contained albumin and hyalin casts, acetone and diacetic acid. Stools were frequent and involuntary; no parasites were found. The blood contained hemoglobin, 70%; R.B.C., 3,300,000; W.B.C., 6800. Blood chemical determinations showed slight increase in non-protein nitrogen on admission. No other abnormal findings. The Wassermann and Kahn tests were negative. Temperature, 100.8° F.; pulse, 120; respiration, 40.

This patient was apparently *in extremis* on admission. She was given a liquid, high-caloric, high-vitamin diet, including 45 gm. of dried brewers' yeast. To this was added 12 cc. of dilute HCl; 1 cc. of liver extract (Lilly, 343-soluble) was given intramuscularly daily. In addition, she was given

10 gm. of ventriculin, 3 times daily, for 2 weeks and for another 2 weeks, 90 cc. of liver extract for oral administration daily. Gastric juice in amounts varying from 100 to 300 cc. was given on 49 of the 51 days of observation. All usual measures for emergency hydration were practised on admission and glucose was administered on many occasions; 300 cc. of blood were given by transfusion on July 13, and again on July 19. This patient remained stuporous or delirious during her entire stay in the hospital. She was constantly and increasingly febrile, temperature reaching 105° F. 50 days after hospitalization. Diarrhea was constant and involuntary. Feeding was always forced and usually by tube. Death occurred on August 5, 51 days after hospitalization. *Autopsy* showed no cause for fever or death. There were the usual atrophic changes in the gastro-intestinal tract which are seen in fatal pellagra.

TABLE 5.—ANALYSES OF GASTRIC CONTENTS.

Date, 1935.	Free HCl.	Total acidity.
June 15	4	7
July 21	16	65

Comment. Observation of similar febrile stuporous cases of pellagra led us to expect an early fatal outcome. All known methods of treatment were employed, and have been previously employed by us except the use of gastric juice. It is a question whether the prolongation of life in this instance was due to gastric juice.

CASE 6.—(No. 97541.) A negress, aged 47, was admitted, June 21, 1935. No definite onset of symptoms could be determined. She had been in failing health for 7 months, with increasing weakness, loss of weight and sore mouth. She was very thin, weighing 103 pounds. There was typical pellagrous dermatitis of the hands, wrists, elbows and knees. The tongue was red and smooth, not ulcerated; there was moderate stomatitis. Diarrhea was absent. Mentality was very poor but not definitely deteriorated. The urine was not abnormal. The stools contained no parasites. The blood contained hemoglobin, 70%; R.B.C., 4,232,000; W.B.C., 5400. Blood chemical determinations were normal. Wassermann and Kahn tests were negative. The temperature was 98.4° F.; pulse, 80; respiration, 20.

TABLE 6.—ANALYSES OF GASTRIC CONTENTS.

Date, 1935.	Free HCl.	Total acidity.
June 22	0	10
July 4	0	0
12	0	10

Subsequent analyses at weekly intervals showed no change in values.

This patient was put on pellagra-producing diet for 2 weeks. No significant change in her condition occurred. On July 4, gastric juice was started and was administered in amounts varying from 80 to 200 cc. for 23 consecutive days. There was steady but not spectacular improvement. On July 20, stomatitis was healed, and the tongue had assumed a normal appearance, dermatitis was exfoliating but not healed. On July 30, when gastric juice was discontinued, all signs of pellagra had disappeared; the weight was 116 pounds. The blood showed some improvement; hemoglobin, 80%; R.B.C., 4,600,000; W.B.C., 9250. Pellagra-producing diet was continued until discharge, on August 7, 1935.

Summary. Six cases of pellagra have been treated with gastric juice in varying amounts given over periods of 10 to 49 days. In 1 instance (Case 1), ground raw beef was incubated with the gastric juice and the predigested beef administered daily for 10 days. Three cases (Cases 2, 3 and 4) of severe pellagra improved more rapidly than our experience would lead us to expect even when optimum diet fortified with vitamin B_2 is administered. One case[6] of moderately severe pellagra improved rapidly and was in complete remission after 23 days. One case[7] of extremely severe febrile comatose pellagra survived for 51 days with the administration of gastric juice. All patients except Case 5 were fed a pellagra-producing diet.

Certain variations, interesting but quite inconstant, were noted in the acidity of the gastric juice during treatment.

Conclusions. The results obtained by administering gastric juice to a small number of pellagrins maintained on pellagra-producing diet would indicate that unusually rapid recovery may take place under this treatment.

It is suggested that there is an intrinsic factor present in normal gastric juice which makes possible the utilization of minimal amounts of extrinsic factor (B_2).

Prolonged remission in at least 2 instances indicates that this intrinsic factor may be stored in the body.

The hypothesis is, therefore, advanced that in pellagra there is an intrinsic deficiency of variable degree. Some individuals retain enough intrinsic factor to recover even on diets grossly deficient in vitamin B_2. Others are able rapidly to regenerate intrinsic factor in the presence of an abundant supply of extrinsic factor and so recover on high-vitamin feeding. Others are totally lacking in intrinsic factor and unable to regenerate it even under optimum dietetic therapy. These may recover under substitution therapy with intrinsic factor or may die of nervous or cardiac damage inflicted before therapy was started.

It is further suggested that the intrinsic factor is exhausted or cannot be regenerated during prolonged deprivation of extrinsic factor.

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STUDIES IN DIABETES MELLITUS.

IV. Etiology. Part 2.*

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Build and Diabetes. Child and adult diabetics show distinct differences, as compared to healthy individuals of the same ages, in regard to build, and this phase must be discussed separately for the two groups.

Height. The adult diabetics have a normal distribution in regard to height (Table 9). The average height without shoes† was 5 feet, 7.2 inches for men and 5 feet, 1.8 inches for women. These measurements are not significantly different from the average heights, with shoes, for males of 5 feet, $8\frac{1}{4}$ inches, and for females of 5 feet, $4\frac{1}{2}$ inches, based on recent insurance data on heights.[21] Allowance must also be made for the fact that the diabetics include a large percentage of foreign-born Jewish patients who tend to be below average height, and also a large proportion of old persons who have already suffered some loss in height due to age.

In children, on the other hand, the height at onset tends definitely to be above the average, so much so that overheight may be con-

* Part 1 appeared in the June issue of this journal.

† Where measurements were taken with shoes, deductions for heels were: 1 inch for men and 2 inches for women.

sidered a distinct characteristic of the diabetic child at the beginning of his diabetes. Before presenting results, it may be well to point out the special precautions which are necessary in analyzing these facts for children. First of all, since we are dealing with the period of active growth, the facts regarding the build of the child are trustworthy only if accurate and periodic records of the child's growth are kept or if the onset of the disease can safely be placed within a very short time of the first examination at which accurate measurements are made. In our analysis given in Table 10 we have included only cases where the height as of the date of onset

TABLE 9.—HEIGHT (WITHOUT SHOES) OF ADULT DIABETICS. PERCENTAGE DISTRIBUTION OF PATIENTS AGED 20 AND OVER AT ONSET. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Males.			Females.		
Feet.	Inches.	Per cent of total.	Feet.	Inches.	Per cent of total.
Total		100.0	Total		100.0
5	2 and under	4.2	4	8 and under	2.3
5	3	4.3	4	9	3.0
5	4	7.1	4	10	6.1
5	5	11.4	4	11	8.2
5	6	12.7	5	0	11.6
5	7	14.1	5	1	13.4
5	8	14.6	5	2	15.8
5	9	11.7	5	3	13.7
5	10	8.4	5	4	10.5
5	11	6.1	5	5	7.2
6	0	2.9	5	6	4.3
6	1	1.3	5	7	2.2
6	2 and over	1.2	5	8 and over	1.7
Average height:		5 feet, 7.2 inches			5 feet, 1.8 inches
Number of cases with known heights:		2,299			2,381

was stated, and was consistent with other (usually later measurements), or, if the height was not given as of onset, the case was used only if diabetes was diagnosed within 2 months of onset. Of 159 boys whose diabetes began before age 20, and who met these specifications, 55.3% were above average height for their age, 16.4% were average height and only 28.3% below average height.* Similarly, of 107 diabetic girls, 58% were above average height, 11.2% of average height and only 30.8% below average height. In girls the proportion of tall height was larger under 15 than over that age.

* The figures cited here are much lower than those previously reported by White[25] for this experience. It is due to the use of severer standards of selection of cases and also of more recent height standards which give higher figures for normal than those used by White.

The standards used were relatively severe, namely, Baldwin's[22] averages of Iowa children at ages under 6 and a group of private school children at ages 6 and over, on whom successive measurements were available over a period of years. A high frequency of overheight in diabetic children at onset was first pointed out by Priscilla White[23] and since has been reported by many observers. John[24] has recently summarized these data.

TABLE 10.—NUMBER OF CASES BELOW AND ABOVE AVERAGE HEIGHT. MALE AND FEMALE CHILD DIABETICS. BY BROAD AGE GROUPS AT ONSET. EXPERIENCE OF E. P. JOSLIN, 1897–1932.

Age at onset (nearest birthday)	Males				Females			
	All heights	Below average height	Average height	Above average height	All heights	Below average height	Average height	Above average height
All ages	159	45	26	88	107	33	12	62
Under 5	29	7	5	17	18	4	3	11
5– 9	46	14	6	26	26	7	4	15
10–14	53	17	7	29	40	8	3	29
15–19	31	7	8	16	23	14	2	7

Maximum Weight Prior to Diabetes. The adult diabetic tends definitely to be overweight at the onset of his disease. The analysis of this experience (Table 11) is based on the per cent departures from average weight, height and age considered, at maximum weight prior to diagnosis of diabetes.* Among males, age 20 or over at onset, 78.5% were at least 5% overweight at the time of their maximum weight and among women, no less than 83.3%. Moreover, 51% of the males and 59.3% of the females were at least 20% overweight, and 16.5% of the males and 25.8% of the females were actually 40% or more above average weight.

This factor of obesity at or prior to onset is one of the most stable characteristics in the medical history of diabetics. When analyzed in four different periods, the proportion of overweights was approximately the same in all four. Among adult males, the proportion 5% or more overweight varied only between 78.1 and 80.1%, and among females, between 80.5 and 86.4%.

Among patients with onset of diabetes in adult life, the proportion who were overweight at their maximum weight is fairly constant at the various ages (Table 11). The only exception is in early adult life, where 59.2% of males were overweight and 64.6% of females, as compared with 78.4 to 84.6% of males in later life and 81.2 to 88.2% in females.

* As we have indicated in the preceding paper,[25] these percentages based on departures from average weight, understate both the frequency and degree of overweight, because these basic averages increase with age. The nature of these increases is such that the average weights at the older ages do not represent the "ideal" weights. Unfortunately, there are no commonly accepted weight standards of that type.

In all these groups, the majority of the remaining cases were of average weight at their maximum. Very few had always been thin people, *i. e.*, at least 20% underweight. Less than 1% were in this group among patients 35 years or over at onset, the proportion being especially small in the case of females. This figure for those 20% or more underweight compares with 1.7%[27] among insured men at the time of acceptance for insurance. The latter figure, however, is somewhat too low for the general population, because some marked underweights are rejected for insurance.

TABLE 11.—MAXIMUM WEIGHT PRIOR TO ONSET OF DIABETES OF ADULT DIABETICS. PERCENTAGE IN GROUPS CLASSIFIED BY DEVIATION FROM THE AVERAGE WEIGHT FOR HEIGHT AND AGE. CLASSIFIED BY YEAR OF EXAMINATION, AGE GROUPS AT ONSET AND SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

	Total.	Year of examination.				Age at onset.				
	1897 to 1928.	1897 to 1914.	1915 to 1919.	1920 to 1924.	1925 to 1928.	20 to 34.	35 to 44.	45 to 54.	55 to 64.	65 and over.
MALES:										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Overweight, total	78.5	79.6	80.1	78.2	78.1	59.2	80.0	84.6	83.3	78.4
20% or more	51.0	52.2	51.1	49.8	51.8	29.5	51.5	59.8	54.6	51.2
40% or more	16.5	15.9	16.0	16.1	17.0	10.6	15.6	21.5	14.7	16.3
30% to 39%	13.9	17.8	13.4	13.1	14.2	5.7	16.5	14.0	16.9	16.9
20% to 29%	20.6	18.5	21.7	20.6	20.6	13.2	19.4	24.3	23.0	18.0
5% to 19%	27.5	27.4	29.0	28.4	26.3	29.7	28.5	24.8	28.7	27.2
Normal weight	13.6	13.4	9.6	14.2	14.4	20.8	13.5	10.9	11.3	15.7
Underweight, total	7.9	7.0	10.3	7.6	7.5	20.0	6.5	4.5	5.4	5.9
5% to 19%	7.1	6.4	9.3	6.7	6.8	19.0	5.7	3.8	4.8	4.7
20% or more	0.8	0.6	1.0	0.9	0.7	1.0	0.8	0.7	0.6	1.2
FEMALES:										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Overweight, total	83.3	86.4	80.5	84.6	82.4	64.6	83.9	88.2	85.7	81.2
20% or more	59.3	75.4	57.2	60.6	57.6	40.0	64.0	65.6	59.7	50.0
40% or more	25.8	28.8	30.1	25.5	24.8	18.2	32.4	29.7	22.8	14.7
30% to 39%	14.2	19.2	10.0	15.1	14.1	10.9	14.9	15.6	14.1	12.8
20% to 29%	19.3	27.4	17.1	20.0	18.7	10.9	16.7	20.3	22.8	22.5
5% to 19%	24.0	11.0	23.3	24.0	24.8	24.6	19.9	22.6	26.0	31.2
Normal weight	10.4	6.8	11.9	8.8	11.7	17.5	9.3	8.1	10.9	11.0
Underweight, total	6.3	6.8	7.6	6.6	5.9	17.9	6.8	3.7	3.4	7.8
5% to 19%	5.5	6.8	7.1	5.7	5.1	15.1	6.3	3.5	2.7	6.9
20% or more	0.8	...	0.5	0.9	0.8	2.8	0.5	0.2	0.7	0.9
NUMBER OF CASES:										
Males	2,251	157	313	793	988	385	474	716	504	172
Females	2,345	73	210	896	1,166	285	443	802	597	218

Patients with onset of diabetes between ages 20 and 35 show an appreciably lower proportion of overweights than those with later onset. The frequency of overweight, even in these younger cases, however, is far above normal. Of the males, 59.2% had been overweight at their previous maximum weight and 64.6% of the females. A large percentage of these cases, moreover, was only moderately overweight. The remaining cases were about evenly divided between normal weight and underweight. Even among these patients, between 20 and 35 years at onset, however, relatively few had been markedly underweight (20% or more). Only

1% of these young male diabetics and 2.8% of the females had always been that much underweight.

Comparison With Other Experiences. The presence of obesity prior to the onset of diabetes is probably the best-known characteristic of the disease. It is, therefore, unnecessary to present in any great detail the findings of other observers. In Table 12 we show, therefore, only 3 other recent experiences,[28,29,30] in comparison with the present one. The basis of the comparison is the percentage of adult patients at least 20% overweight and the percentage at least 30% overweight at the maximum prior to diagnosis of diabetes. It is notable that 2 of the 3 show considerably higher percentages of overweights prior to diabetes than the present one and the lower incidence of overweight in the third group is probably due to the inclusion of a fairly high percentage of children among whom, as we shall see later, obesity is relatively uncommon. A striking feature in all experiences is the greater frequency of overweight among diabetic women than men.

TABLE 12.—MAXIMUM WEIGHT OF ADULT DIABETICS PRIOR TO DIAGNOSIS. PERCENTAGE OF PATIENTS AT LEAST 20% AND AT LEAST 30% OVERWEIGHT. BY SEX. RECENT CLINICAL EXPERIENCES.

	Per cent.			
	20% or more overweight.		30% or more overweight.	
	Males.	Females.	Males.	Females.
Joslin	51.0	59.3	30.4	40.0
John[28]	76.0	78.8	56.1	68.2
Adams[29]	68.8*	...	51.9*	...
Palmer[30]†	40	52	24	30

* Both sexes combined.
† Includes children.

Weight of Jewish Patients. In Jewish adult patients, the tendency to obesity is even more marked than among other patients. The proportion of diabetic Jewish men who were overweight at their maximum prior to diagnosis was 86.8%, compared with 78.5% for all adult males in this experience. Among Jewish women, no less than 94.3% were overweight at their maximum, compared with 83.3% for all female diabetics. More of the Jewish patients were very stout, particularly the women. Of the diabetic Jewish men, 58.4% were at least 20% overweight as against 51% for total males, and of the Jewish women, 77%, compared with 59.3% for total females. The proportion of the actually obese (40% or more overweight) was about the same for the Jewish men (16.2%) as for all males in this experience (16.5%). Among Jewish women, however, 33.5% were obese, compared with only 25.8% for all

of the diabetic women. The majority of the remaining Jewish patients were of average weight. Only 2 of the Jewish adult patients had always been thin, 1 male and 1 female, both of whom were under age 35 at onset.

The excessive proportion of overweights among Jews is found at every age. The excess is particularly large, however, among patients with onset between ages 20 and 45. As in the case of non-Jewish diabetics, however, the proportion of Jewish patients who had been previously overweight was lower for those with onset at ages 20 to 35 than at later ages.

TABLE 13.—WEIGHT OF CHILD DIABETICS UNDER AGE 20 AT ONSET OF DISEASE. BY SEX AND AGE. EXPERIENCE OF E. P. JOSLIN, 1897–1932.

Sex; age at onset.	Per cent.					Total number of cases.
	Overweight.		Average weight.	Underweight.		
	Moderate.	Slight.		Slight.	Moderate.	
MALES:						
Total	9	9	48	20	14	100
Under 5	4	18	64	14	..	22
5–9	11	..	59	15	15	27
10–14	13	11	37	18	21	38
15–19	..	8	31	46	15	13
FEMALES:						
Total	12	10	32	28	18	76
Under 5	..	15	54	23	8	13
5–9	11	5	42	21	21	19
10–14	9	12	23	35	21	34
15–19	40	10	10	20	20	10

Basis of weight classification for overweight and underweight is deviation from average weight.

	Under 5	5 to 9	10 to 19
Slight	4 to 6 pounds	5 to 8 pounds	5 to 14%
Moderate	7 pounds or more	9 pounds or more	15% or more

Weight standards: Under age 5, Woodbury; ages 5 to 19, Baldwin and Wood.[31]

Weight of Children. Diabetics with onset during childhood and adolescence in contrast with older diabetics do not show a high frequency of overweight. Entirely different standards for measuring the degree of overweight are necessary for children, because each pound departure from average weight may represent a deviation of as much as 4%. On the basis of the standards adopted, which are described in Table 13, 48% of the diabetic boys and 32% of the girls were average at their maximum. Moreover, there were twice as many who were underweight as were overweight, both among boys and girls. Excessive weight was relatively infrequent.

The details are shown separately for 5-year age periods in the table. They show some variations from the general situation described, but these differences are not consistent and seem to be due to the small number of cases involved. Joslin, Root and White,[23] Boyd and Nelson,[32] Spencer[33] and others report similar results in their series of diabetic children.

The difference in the build picture of child and adult diabetics is significant. In the case of the child a vertical overgrowth is typical, whereas in the adult it is lateral. It is likely, however, that these two types of overgrowth correspond and both are believed to be essentially of the same nature, namely, of endocrine origin. Before discussing this aspect of the situation, however, it is necessary to review other pertinent facts in the medical history of diabetics.

Incidence of Thyroid Abnormalities. The most distinct clinical evidence of multiglandular etiology of diabetes is the frequency of thyroid abnormalities, especially hyperthyroidism, among diabetics. These cases have been studied intensively by the senior author since 1921,* At the outset the difficulty of correct diagnosis of diabetes associated with hyperthyroidism must be stressed. Glycosuria and, to a less extent, hyperglycemia are frequent in hyperthyroidism, and it is often hard to tell whether the disturbed metabolism is really diabetic. For this reason it may be advisable to raise the standards of diagnosis of diabetes in hyperthyroidism. In addition, therefore, to the figures based on normal standards, others are shown in the text, in parentheses, in which the level of the blood sugar was at least 0.15% fasting and 0.2% after food and with glycosuria also present. On this basis, 1.1 (1) % of the males and 3.3 (3) % of the females, first seen during 1921 to 1928, gave a history of hyperthyroidism or had it when examined. None of these patients was under age 20 when first seen. Among males the proportion of hyperthyroid cases was low at every age, but among females there was a decided peak between the ages of 35 and 44, with 8.2 (7.2) % having a history of hyperthyroidism. Most of the hyperthyroid cases, both male and female, were between the ages of 20 and 54, constituting 1.9 (1.6) % of the total men and 5.6 (5.1) % of the total women in this broad age group. These percentages are believed to be higher than normal, but just how much is difficult to say because no good standards exist by which to measure the normal frequency of hyperthyroidism. It varies from place to place, the so-called "goiter belts" showing high rates. In the northeastern section of the country from which most of these cases are drawn, toxic goiter is not especially prevalent. Figures in the present experience are higher than those reported by most observers,[30,34,35] but the data are scanty and do not warrant repro-

* In coöperation with F. H. Lahey. This experience since 1921 includes many diabetics among Lahey's surgical thyroid cases and overstates somewhat, therefore, the incidence of such cases among diabetics.

ducing here. John[31] has summarized some of these experiences. Most of them are in agreement with the present one in regard to the high proportion of diabetic women with hyperthyroidism, as compared with male diabetics. It is significant, moreover, that where goiter generally is most prevalent, the proportion of diabetics with hyperthyroidism is high.

Minor thyroid abnormalities (moderate or marked enlargements; fullness; palpable thyroid and previous thyroid surgery, cause unknown) were much more frequent in this experience than hyperthyroidism. Among males 2.9% and among females 6.8% showed such abnormalities. The proportions tended to be highest during adolescence and early adult life and lower at the older ages. At every age they were higher among females than males. These findings characterize non-toxic thyroid disease generally. The percentage of these cases among diabetics appears to be relatively high, but accurate measurement of the excess is impossible to make because of differences in classification and in geographical distribution of thyroid abnormalities of this type.

Pituitary Gland. There are striking clinical findings which suggest that the pituitary gland may influence the onset or course of diabetes. That diabetic adults are overweight and diabetic children are overheight prior to the onset of diabetes points strongly to the operation of a pituitary factor. It is well recognized that glycosuria and diabetes are extremely common in acromegaly. Furthermore, we know that pituitary extract and insulin are antagonists. When extracts of the anterior lobe of the hypophysis are injected into a normal dog, temporary glycosuria, hyperglycemia and hyperlipemia develop. The work of Houssay[36] and his associates is of particular significance. These workers showed that removal of the hypophysis lessens greatly the severity of the diabetes in totally depancreatized animals.

Suprarenal Glands. It has long been understood that the suprarenal glands exert an influence over carbohydrate metabolism. Such knowledge, however, has been concerned largely with the effect of adrenalin, the secretion of the medullary portion of the gland. This substance causes glycogenolysis in the liver, and in this way acts as an insulin antagonist. Attempts to ameliorate severe diabetes by adrenalectomy or section of the splanchnic nerves have had this relationship as a basis.

More recently a new field has been opened up by the work of Long and Lukens,[37] who have shown that when bilateral total adrenalectomy is carried out in totally depancreatized cats, the diabetes becomes much milder, resembling that of the hypophysectomized animals in the Houssay experiment. The total adrenalectomy stops the breakdown of protein and abnormal production of ketone bodies which are characteristic of diabetes.

The Incidence of Gall Bladder Disease. Gall bladder disease as

a precursor to diabetes has been reported often in the medical literature. The chief causes suggested are disturbed lipoid metabolism, especially in relation to gall stones, and infection of the gall bladder, subsequently involving the pancreas. In this experience a previous history of gall bladder disease is common among adult diabetics, particularly women. In the period 1897 to 1928, 2.6% of the men gave such a history. Of these, 1.5% had had gall stones and 1.1% inflammation of the gall bladder or other symptoms of gall bladder disease. Women with such histories numbered 7.6% of the total, of whom 4.7% gave a definite history of gall stones and 2.8% had had cholecystitis or other evidence of gall bladder disease. Such histories subsequent to examination were likewise fairly frequent.

The true incidence of gall bladder disease is probably understated by the figures relating to the whole period, for analysis of the data shows that the incidence is higher among patients seen in recent years, probably due to more careful attention to this factor in taking case histories. Thus, in the four years ending in 1928 the proportion with biliary tract disease was 3.6% for men and 9.9% for women, proportions so high as to suggest a close relationship between the two conditions. We must admit, however, that gall bladder disease has not been prominent as a cause of death. In the period 1922 to 1935, of 2415 deaths of diabetics, only 11 were ascribed to gall bladder disease by the attending physician.

Age has a decided bearing on the frequency of gall bladder disease. Among men the proportion is decidedly below the average up to age 45, but then jumps and increases slightly thereafter with advancing age. The proportion is highest in those with onset of diabetes at ages 65 and over, when it reaches 4.6%. Among women, a sharp increase in the proportion of gall bladder cases takes place at age 35, or 10 years earlier than in the case of men. The proportion giving a history of gall bladder disease remains fairly constant thereafter in the case of women. The maximum proportion among them, however, in the whole experience is found between the ages 60 and 65, where 9.7% gave a history of gall bladder disease, but in the period 1925 to 1928 the peak occurred between ages 45 and 50, with 13.3% reporting gall stones or symptoms of biliary disease.

Practically all of the diabetics with a history of gall bladder disease were overweight prior to their diabetes. Of the 71 males, only 7 were within normal limits at their maximum weight prior to diagnosis, and only 4 underweight, but none as much as 20%. Likewise, among the 219 women with gall bladder disease, only 13 had been average weight at their maximum before diagnosis and only 3 had always been underweight; none of them, however, as much as 20%. The proportion of gall bladder cases among all overweight men, in this experience, was 3.1%, compared with 2.3%

for both normals and underweights. Among women, however, the differential was even larger, with 8.5% of the overweights reporting gall bladder disease, compared to 5.3% for normals and 2% for underweights. The proportion of gall bladder cases among overweights did not show any significant trend in relation to the degree of overweight. The obese reported only a slightly greater proportion of gall bladder cases than the moderate overweights.

Jewish patients did not differ markedly from other patients in the proportion reporting a history of biliary tract disease. There was a slight excess in the case of females. The proportion for Jewish women was 8%, compared with 7.6% for all women during the entire period, 1897 to 1928. In recent years, 1925 to 1928, the proportions were 10.6% and 9.9%, respectively. The weight characteristics of Jewish diabetics with gall bladder histories differs not at all from those observed among all patients with this history.

Despite the high frequency of gall bladder disease among these diabetics, it is questionable whether the figures are really significant. The disease is a fairly common ailment in adult life. In one clinic[38] such conditions were reported in 6% of the patients over age 20. The incidence in serial autopsy studies is about 10 times as high.[39,40] Stones are present in one-fifth to one-half of these cases, the higher proportions being present at the older ages. Most of these cases, of course, give no symptoms during life. Moreover, gall bladder lesions are notoriously common among the obese and, since most diabetics are overweight before the onset of their disease, a high frequency of gall bladder disease would be expected. Dublin, Jimenis and Marks,[41] in a study of insured persons with a history of gall bladder disease, all free of diabetes when they were examined for insurance, found a large proportion, especially of the women, to be overweight. In addition, analysis of the subsequent mortality of the group showed a low incidence of diabetes up to the closing date of their study. Beaser,[42] in a study of Vanderbilt Clinic records, found that gall bladder disease proved by operation or autopsy was equally frequent in diabetic women and a control group, and the proportion of cases with gall bladder disease diagnosed from the symptoms was even greater in the control group. His analysis was limited to ages 40 to 65 and, in the case of the diabetics the gall bladder histories were limited to those preceding the diabetes.

Arteriosclerosis. Arteriosclerosis, resulting in inadequate blood supply to the pancreas, has been suggested as one of the causative factors in diabetes, particularly in the aged. The proneness of the diabetic, especially when inadequately treated, to develop arteriosclerosis prematurely is well known and consequently the incidence of arteriosclerosis among diabetics without regard to the duration of the disease is likely to lead to erroneous conclusions. Consideration may be given, however, to the incidence of arterial change as an etiological factor in those cases which, so far as can be determined,

were of relatively recent origin, that is, diagnosed within 1 year of onset. Analysis has been made of the incidence and degree of sclerosis of the peripheral arteries disclosed by palpation of the radial artery at examination in all such cases in this experience, but the data are most reliable and consistent for cases first seen beginning July 1, 1927, since which date a classification of arterial change based upon Pratt and Bushnell's[43] description has been used. This method distinguishes the degree of abnormality of the radial arteries as follows: 0, none; 1, palpable; 2, roll under finger; 3, tortuous; and 4, beaded or pipestem. The last two groups, the severer grades, seem to be comparable with classifications used earlier than July 1, 1927, and these earlier results are used.

TABLE 14.—INCIDENCE AND DEGREE OF SCLEROSIS OF RADIAL ARTERY AT EXAMINATION AMONG DIABETICS SEEN WITHIN 1 YEAR OF ONSET. PER CENT OF CLASSIFIABLE CASES. BY SEX AND AGE GROUPS AT EXAMINATION. EXPERIENCE OF E. P. JOSLIN, 1922 TO 1928.*

Sex; degree of arteriosclerosis.	July 1, 1927 to 1928.							August 7, 1922 to 1928.						
	All ages.	Under 20.	20 to 39.	40 to 49.	50 to 59.	60 to 69.	70 and over.	All ages.	Under 20.	20 to 39.	40 to 49.	50 to 59.	60 to 69.	70 and over.
MALES:														
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0							
0	26.2	94.4	37.1	20.0	7.3	...	...							
1	24.4	5.6	42.9	37.1	23.6	22.5	10.0							
2	29.5	...	14.3	37.2	50.9	40.0	15.0							
3	14.9	...	5.7	5.7	16.4	30.0	40.0	11.9	...	1.3	8.4	15.1	26.4	43.9
4	5.0	...	...	...	1.8	7.5	35.0	4.0	...	...	0.9	2.6	9.4	29.3
FEMALES:														
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0							
0	44.9	94.9	75.7	51.2	21.3	11.9	7.1							
1	28.0	5.1	21.6	37.2	41.0	31.0	14.3							
2	22.0	...	2.7	11.6	32.8	42.8	57.2							
3	4.7	...	...	...	4.9	14.3	14.3	6.9	...	...	1.6	8.6	18.3	17.5
4	0.4	...	...	...	...	...	7.1	0.4	...	...	...	0.5	0.8	2.5
NUMBER OF CASES CLASSIFIABLE:														
Males	221	36	35	35	55	40	20	674	118	150	107	152	106	41
Females	236	39	37	43	61	42	14	711	120	111	122	187	131	40

* Classification based on Pratt's description since July 1, 1927. Data prior to that date comparable only for Grades 3 and 4.

The analysis in Table 14 of cases with diabetes of less than 1 year's duration who were first seen after July 1, 1927, shows that among 221 males, 26.2% were free of arterial change; 24.4% had Grade 1 abnormalities; 29.5%, Grade 2; 14.9%, Grade 3; and 5%, Grade 4. Among 236 females, arteriosclerosis was less frequent, particularly the severer grades. Actually 44.9% of these women had normal arteries; 28.0% had Grade 1 abnormalities; 22.0%, Grade 2; 4.7%, Grade 3; and only 0.4%, Grade 4.

In both sexes, practically all the patients under age 20 with diabetes of less than 1 year's duration were free from any signs of arteriosclerosis, only 4 out of 75 cases showing Grade 1 abnormalities

and none, of any greater degree. This picture changes very rapidly with age, however, particularly among males. Every male diabetic past 60 showed abnormalities of at least Grade 1, and the proportions with changes of Grades 3 or 4 reached 18.2% among those patients between 50 and 59, 37.5% at ages 60 to 69 and 75% at ages 70 and over. Among females, the percentages were much lower. Indeed, 21.4% of the diabetic women 70 or over at examination had no or slight abnormalities of the radial arteries and a like proportion, severe abnormalities (Grades 3 and 4). The figures on severer types are confirmed by the more extensive series of observations based on all first-year cases seen from the beginning of insulin treatment in 1922 down to the end of 1928.

The figures for these diabetics display the usual age relationships in arterial changes, but they are far above normal, particularly in the case of males. Comparison with supposedly typical samples in the population is not altogether accurate, however, because of differences in standards used, and this limitation should be kept in mind in the comparisons that follow. Sydenstricker and Britten[44] found that the percentage of males with normal arteries was 88.6% at 20 to 24; 83.6 at 30 to 34; 72.3 at 40 to 44; 56.1 at 50 to 54; and 43 at 60 to 64. By far the largest proportion of those with arterial thickening showed very slight abnormalities and even between 60 and 64 only 18.6% showed moderate or marked thickening. In their series,[44,45] practically no sex differences were found in the percentage showing arterial thickening, whereas among these diabetics, the male rates were distinctly higher than those for women. Because diabetics are generally overweight before onset of their diabetes, it is fairer to compare the frequency of arterial change among them with that of a typical series of overweight persons, but unfortunately such data on overweights are unsatisfactory because the usual method of palpating the radial artery leads to understatement of the arterial changes in fat persons. As a result, in the series[46] reported by Britten, as well as in another series reported by Dublin, Fisk and Kopf,[47] arterial thickening was found more frequently among the underweights than overweights. This is contrary to the actual situation as revealed by the statistics on build in relation to mortality from causes which are of arteriosclerotic origin.

Obviously, however, data on changes in the peripheral arteries are at best only a rough index to arteriosclerosis elsewhere in the body and, more particularly, in the pancreas. The concept of a truly generalized arteriosclerosis is largely discounted today. Moreover, although sclerosis of the arteries of the pancreas is involved in a considerable percentage of the cases, it is not necessarily diffuse or severe enough to interfere seriously with the function of the organ. Reliable data can only be secured from autopsy studies. Among 259 diabetic deaths in the present series in which the pancreas was available for study at autopsy, Warren[48] reported marked

arteriosclerosis of the pancreas present in only 5%. This figure includes cases of all durations of diabetes and it is likely that the condition is even rarer in newly developed cases. Warren's figure is much lower, however, than that of Wartman,[49] who, for a general experience, reported marked arteriosclerosis of the pancreas in 22.3% of the cases at all ages and at ages past 60, in 45.7% of the men and 31.8% of the women. Root and Sharkey[50] compared 175 diabetic and 175 non-diabetic autopsies and found that patients with diabetes of less than 1 year's duration showed no more arteriosclerosis than non-diabetic cases of similar age. On the other hand, diabetics of longer duration showed far more extensive arteriosclerosis than non-diabetics.

The wide differences in the figures quoted make it difficult to draw any positive conclusions on arteriosclerosis as an etiological factor in diabetes, despite the high incidence of peripheral arteriosclerosis in diabetes, particularly among males. The picture is rather confused. One can say definitely, however, that arteriosclerosis is not a factor in the causation of diabetes in childhood, and very improbably a factor in adults up to age 40. After that age, the question is still open and further investigation is necessary to clarify it.

Cancer of the Pancreas. Cancer of the pancreas is undoubtedly a cause of diabetes in a small proportion of cases. Among patients first seen between 1897 and 1928, there have been 28 who had primary cancer of the pancreas, and 1 patient with a secondary cancer of the pancreas. They constituted 13.4% of all patients with cancer, as compared with 2%* in the general population. The full importance of cancer of the pancreas is unknown, because it is not usually diagnosed at the time of examination for diabetes.

Summary. 1. A representative group, of 6357 private diabetic patients (treated by Joslin in the office or hospital or by consultation over a period of 30 years) and of 463 diabetic children seen more recently, is described together with an analysis of various etiological features of the disease, which lend themselves to statistical interpretation.

2. The residence of 85% of the patients was in New England, 67% in Massachusetts, 41% in the Boston Metropolitan District and 14% in Boston itself.

3. American nativity characterized approximately two-thirds of the adult patients; one-sixth of the patients were Jews, although but one-twelfth of the population in the area from which they came was of that race.

4. Occupations were diverse, but there was a rather large proportion of proprietors, officials, managers and members of professions. Physicians alone amounted to 6.9% of 2304 patients whose occupations were definitely recorded.

* Based on deaths only.

5. Most of the patients were first examined because of symptoms of diabetes, but a large number were diagnosed as a result of routine examinations. Insurance was the chief of these and accounted for the recognition of 12.6% of the males. The number of cases diagnosed after application for insurance has steadily increased.

6. Males exceeded females until 1922, but since that date the situation has been reversed and the disparity is definitely increasing.

7. The number of cases increased steadily from infancy to a maximum at ages 50 to 54, except for a slight dip in the late teens, and dropped rather sharply from the peak in old age. There has been a definite increase in recent years in the proportion of patients at the older ages: past 60 among males and past 50 among females. Comparative data are given for other diabetic series. Analysis with regard to the true incidence of age at onset of diabetes shows that onset is most frequent in the sixth decade, and next highest in the seventh decade.

8. Jewish patients develop diabetes relatively young. The median age at onset of the Jewish patients was more than 2 years younger than that of all patients. Jewish female patients exceeded the males up to the end of 1928 by 46.3% and in the late forties and fifties, by nearly 2 to 1.

9. The present series of cases partially confirms the New York City data of Mosenthal and Bolduan, which show that the incidence of diabetes in married women is higher than in single women. No difference, however, was found between single and married men. The frequency of onset among women in the late forties or fifties reflects the strain on the endocrine system during menopause when gain in weight is also usual.

10. The height of diabetic children at onset tends definitely to be above average, but there is a normal distribution of height of diabetic adults.

11. The weights of adults in this group at onset of the disease were definitely above standard. Among males age 20 or over at onset, 78.5% were at least 5% overweight at the time of their maximum weight, and among women, no less than 83.3%. In children and adolescents, on the other hand, twice as many were underweight as overweight.

12. In Jewish adult patients, the tendency toward obesity was even more marked than among other patients. Of the Jewish men, 86.8% were overweight and 94.3% of the Jewish women.

13. Hyperthyroidism was present in 1% of the males and 3% of the females first seen during 1921 to 1928.

14. The influence of the pituitary and adrenal glands upon diabetes is discussed.

15. A history of biliary tract disease was reported by 3.6% of the men and 9.9% of the women first seen in 1925 to 1928. Practically all of the diabetics with gall bladder disease were overweight.

16. Arteriosclerosis was practically absent in diabetics under age 20 whose diabetes was of less than 1 year's duration. It increased with advancing age until at ages 60 and over every male diabetic exhibited it in some degree.

17. Cancer of the pancreas is a cause of diabetes in a small percentage of cases.

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TREATMENT OF DIABETIC COMA.

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A considerable mortality still exists in patients with diabetic coma, despite the introduction of insulin. In a recent series of cases of diabetic coma treated in Joslin's Clinic, Marble, Root and

White[1] report a mortality of 11%. Eight deaths similar to those reported by the above authors have occurred in this hospital since 1928.* We believe that death in these cases was due to the loss of a large part of the alkali reserve of the body (mainly sodium) and that its replacement would have reduced the mortality considerably.

All investigators now agree upon the general principles involved in the treatment of diabetic coma, since insulin has become the major tool in the treatment. Of primary importance is the relief of the organic acidosis, or ketonemia, brought about by incomplete oxidation of fats; which, in turn, is the result of insufficient oxidation of carbohydrate. We are concerned, then, at the moment, with the presence of the ketonemia and not the hyperglycemia. Hyperglycemia, *per se*, is never the immediate cause of death nor the cause of serious symptoms. The only known detrimental effect of hyperglycemia is a temporary reduction in the inherent ability of the organism to utilize glucose. The only immediate reason for oxidizing glucose is to promote complete oxidation of fat. This is accomplished by the use of sufficient amounts of insulin. Thus, the ketonemia can be abolished.

The other important disturbance, dehydration, which has resulted from lack of fluid intake, vomiting and acidosis, is combated by the administration of large amounts of fluid, usually in the form of physiologic saline parenterally. These measures (administration of sufficient insulin and fluid) are usually successful in the treatment of diabetic coma.

But the occurrence of another state, which if not recognized and treated will quickly end fatally, demands attention. This condition should always be suspected when the signs of acidosis and coma persist after ketonuria has been abolished. These are the cases which are commonly called "insulin resistant" or are said to have been in coma too long to permit the possibility of recovery.

Broadly, what may cause acidosis? Normally, the pH of the blood plasma is 7.4† At this pH there are 20 parts of base bicarbonate ($BHCO_3$) to each part of carbonic acid (H_2CO_3) in the blood plasma.[2] Base (B) represents a total of the basic elements in the blood (Na, K, Ca, Mg) of which sodium makes up over four-fifths. Thus, we have the equation $\frac{BHCO_3}{H_2CO_3} = \frac{20}{1} =$ pH 7.4.

* It is not the purpose of this paper to present a statistical report of cases treated in the manner outlined. It is desired to express a point of view and to indicate the scientific data available in its support.

† Simply stated, pH is a negative logarithmic designation of the hydrogen-ion concentration of the fluid or solution considered. Thus the logarithmic designation of 7 is an abbreviation for 10^{-7} or 0.0000001. In the case of hydrogen-ion concentration this means 1 gm. of hydrogen ions in 10 million gm. of water. Water is very slightly ionized. Since the number of hydrogen ions necessarily equals the number of hydroxal ions, water is neutral. The concentration of either hydrogen or hydroxyl ions in pure water is 10^{-7}. This represents a pH of 7 or a p(OH) of 7.

It is obvious that anything which causes a decrease in $BHCO_3$ or an increase in H_2CO_3 will cause a shift of the pH of the blood toward the acid side. This is expressed in the Henderson-Hasselbalch equation $pH = 6.1 + \log \frac{BHCO_3}{H_2CO_3}$.

1. *Increase in H_2CO_3.* This condition is found in patients where there is interference in the gaseous exchange in the lungs, as, for example, in bronchial asthma or emphysema of the lungs. The symptom complained of is dyspnea on exertion because a sudden increase of carbon dioxid to be disposed of rapidly cannot be adequately driven out of the lungs. Thus there is an increase of H_2CO_3 of the blood. This, of course, represents a mild degree of acidosis.

2. *Decrease in $NaHCO_3$.* This may occur in one of two ways: (1) A direct loss of $NaHCO_3$ from the body, such as occurs in diarrhea, will lower the total alkali of body; (2) a replacement of the bicarbonate ion (HCO_3) by an increase of other acid radicals—such as chlorid, phosphate, sulphate, lactate or the incompletely oxidized fatty acids diacetic or beta hydroxybutyric—will lower the total amount of $NaHCO_3$.

What are the normal defense mechanisms of the body for the prevention of acidosis? There are three main defenses: the blood buffer system, the pulmonary system, and the renal system.

1. *Buffer System.* The sodium bicarbonate ($NaHCO_3$) and sodium phosphate (Na_2HPO_4) buffer system, in the presence of a strong acid, act by the formation of a weak acid and a neutral salt. This allows the pH of the blood to shift only very slightly toward the acid side.

(*a*) $NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3$.

(*b*) $Na_2HPO_4 + HCl \rightarrow NaCl + NaH_2PO_4$.

Protein, being an amphoteric substance, may act as an acid or a base, depending upon its environment. As the pH of the blood shifts toward the acid side, less and less of the protein acts as an acid, thus liberating base to combat the acidity.

2. *Pulmonary System.* When a strong acid enters the body it causes the decomposition of $NaHCO_3$ to make its own sodium salt and liberates carbon dioxid. The lungs then increase their ventilation to expel the newly formed carbon dioxid and in addition rid the body of some of the preëxisting carbon dioxid. This prevents the pH of the blood from dropping as low as it would if the preëxisting carbon dioxid had remained constant. This mechanism adjusts for finer changes in pH but becomes inadequate for large changes.

3. *Renal System.* In severe acidosis the buffer and pulmonary systems are overtaxed and become inadequate and renal activity comes into play. There are two important functions of a normal kidney in the face of severe acidosis, as is well shown by the work of Gamble, Ross and Tisdall:[3] (1) A normal kidney is able to secrete urine at a pH of 5. In the stage of activity 5% of the diacetic

acid and 20% of the beta-hydroxybutyric acid pass unneutralized by base, thus conserving base. (2) The kidney begins to manufacture ammonia so that the acid radicals may be excreted as ammonium salts; thus also conserving base. In this way a normal kidney practises base economy.

Let us return now to the question being considered. Having administered fluid to combat dehydration and having given sufficient insulin to completely abolish ketonuria, what is the mechanism for the persistence of all of the signs of acidosis and coma with a continued low CO_2 combing power?* Richardson[4] reports a case with exactly these conditions. He suggests three possibilities in explanation:

1. That loss of base from the body accompanying a severe dehydration results in an alkali deficit.

2. That most of the ketone bodies are excreted in these cases in the form of beta-hydroxybutyric acid. (Our clinical tests show only the presence of acetone and diacetic acid in the urine.)

3. That perhaps the kidney shuts down entirely on the excretion of ketones but that they remain in high concentration in the blood.

Hartmann,[5] however, has done blood analyses to determine ketone body content in such states and finds a negligible quantity. In some cases he has administered sufficient insulin to bring the blood sugar to hypoglycemic levels. He then finds very little organic acid in the blood but the CO_2 combining power remains low. He states, "It seems apparent, therefore, that much of the base released by organic acid on oxidation is claimed by acid other than carbonic or is excreted from the body." Accordingly, continuation of acidosis and coma is not due to a persistence of ketonemia (organic acidosis).

The difficulty lies in the fact that the last defense of the body, the renal system, has been overwhelmed by the severe acidosis and there has been a continued drainage of base from the body. The alkali reserve of the body has been depleted and a condition of "inorganic acidosis" exists. First, the normal kidney does not begin the manufacture of ammonia in increased quantities until the supply of readily excretable base is diminished; that is, until there is a physiologic need of the body to conserve base. Therefore, from the very onset of acidosis, the body has lost some of its readily available base in trying to excrete the organic acids which were rapidly accumulating. Folling[6] has shown that in experimental acidosis ammonia excretion is very little accelerated the first day, even though the pH of the blood may fall to 7.1. But later, as the available base falls, ammonia production increases. When ammonia production finally reaches its maximum (about 10 gm. of ammonia in 24 hours) it is not sufficient in amount to prevent further

* The CO_2 combining power represents the "alkali reserve" of the blood and reflects directly the "alkali reserve" of the body.

loss of base because of the very large amounts of organic acids which are being presented to the kidney for excretion.

Finally, the kidney temporarily loses its function to make ammonia or to produce a very acid urine. It is common to note the presence of albumin, casts and red blood cells in the urine of patients in diabetic coma with dehydration. Along with the urinary signs of renal damage there is often a rising blood non-protein nitrogen (N.P.N.), oliguria and sometimes anuria. All of these signs disappear when the acidosis and dehydration are corrected. The injury to the kidney has been attributed by various authors to the accompanying severe dehydration and to the toxic effects of the severe acidosis. Coburn[7] recognizes and stresses the importance of temporary renal insufficiency in diabetic coma. The reduction in ammonia production, then, allows more sodium to be excreted in combination with eliminated acid radicals. Linder[8] fed hydrochloric acid to a group of people with normal kidney function and to a group of nephritics and measured the ammonia and sodium excretions in both groups. Invariably the nephritic group excreted much more sodium and less ammonia than did the normal group.

As a final insult oliguria or anuria develops as a result of the dehydration. The kidney is then not able to excrete all of the waste products as is evidenced by the retained N.P.N. in the blood. The other normally excreted inorganic acid radicals, phosphates and sulphates (products of protein metabolism) are also retained. In the blood stream these combine to form their sodium salts at the expense of sodium bicarbonate. If the alkali reserve is then measured by determining the CO_2 combining power of the blood, it is found to be extremely low.

If, besides the mechanisms considered above, the diabetic patient has had some preëxisting renal damage, it is apparent that a much more severe inorganic acidosis might develop. If the alkali reserve is measured in a patient with chronic nephritis and mild renal retention, it is found to be relatively low. In uremia the administration of sodium bicarbonate will often bring the patient temporarily out of the unconscious state and relieve the air hunger.

Therefore, in severe and prolonged diabetic coma with marked dehydration, one is dealing with a total decrease of the sodium of the body and a total increase in the fixed inorganic acids, sulphates and phosphates. Much of the base which was able to be retained in the body is tied up in the form of these inorganic salts at the expense of sodium bicarbonate. Having administered insulin, some sodium is liberated by the disappearance of the ketone acids. But, while a small amount may form sodium bicarbonate, most of the sodium is immediately taken up in combination with the rapidly accumulating sulphates and phosphates.

If, after large quantities of fluid have been given to combat dehydration and the body has been rid of ketone acids by the

administration of sufficient insulin, signs of acidosis (Kussmaul respirations, etc.) and coma continue, the patient is in imminent danger of death. The CO_2 combining power is found to be low and the state of "inorganic acidosis" exists. The pH of the blood must be quickly brought back to normal and the alkali deficit relieved. In this state sodium bicarbonate* should be administered without delay. The response is frequently dramatic. Kussmaul respirations change quickly to a normal type and coma rapidly disappears.

Lemann[9] observes that recovery from coma usually runs parallel to the rise of the CO_2 combining power and the disappearance of ketonuria. Haines and Davis[10] warmly endorse the use of sodium bicarbonate as an adjunct to insulin and use 1000 to 1500 cc. of a 5% solution by duodenal tube. They have never seen harmful results. Campbell,[11, 12] and Hartmann[5] for many years have advocated the use of alkali therapy as an addition to the well established treatment of diabetic coma.

In the recent paper from Joslin's Clinic, referred to above, Marble, Root and White[1] report 55 treated cases of diabetic coma. Six of these patients died in diabetic coma despite the usual treatment. Alkalis are not used in that clinic. Four of the cases died within 4 to 13 hours after admission with low CO_2 combining powers, marked dehydration and shock, oliguria or anuria. The diacetic acid in the urine varied from none to a trivial amount. This we believe to be the small group of cases where there is a definite indication for the use of alkalis.

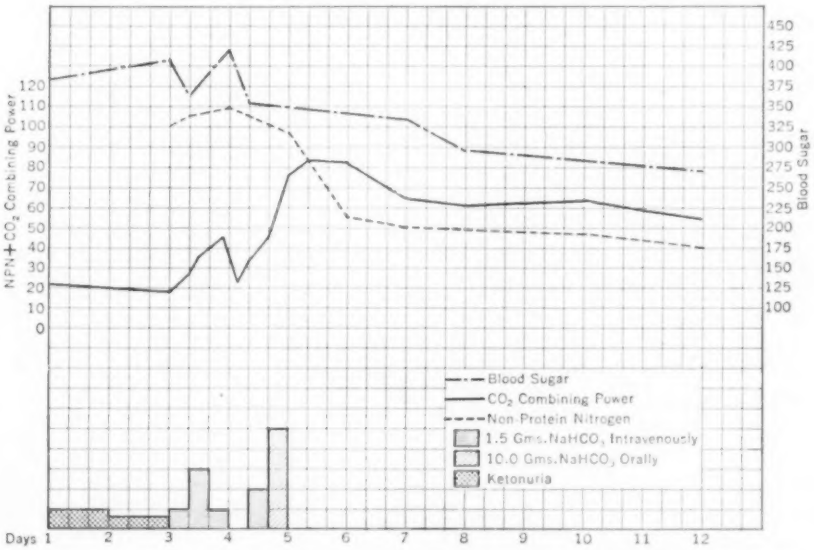
The following case illustrates some of the problems discussed:

Case 1.—A 55-year-old woman had been known to be diabetic for 3 years before admission. Her diabetes had been uncontrolled over this period. She had lost 80 pounds in weight (210 to 130 pounds). One week before admission both she and her husband had become ill after eating oysters. The husband had abdominal cramps and diarrhea which lasted for 2 days. The patient had nausea, vomiting, abdominal cramps and diarrhea. These symptoms gradually became more marked. For 4 days before admission she retained no food or fluid. Twelve hours after admissions she became semicomatose. She had received 10 units of insulin 3 hours before admission to the hospital.

On examination she was found to be deeply comatose. She was severely dehydrated. Respirations were typically Kussmaul. No tendon reflexes could be elicited. The Babinski sign was absent. The urine showed ++++ sugar, ++++ reaction for diacetic acid, ++ albumin, a few red blood cells, and occasional granular casts. The blood sugar was 378 mg. %, CO_2 combining power 21 volumes %, and N.P.N. 100 mg. %. Physiologic saline was administered on admission. She received a daily average of 3500 cc. intravenously for the first 4 days. Thereafter intravenous fluids

* Sodium bicarbonate, 1.5 gm. in 20 cc. of water, can be obtained in sterile ampules ready for intravenous use. A solution of sodium bicarbonate isotonic with the blood contains 13 gm. per liter. The usual dose recommended to bring the CO_2 combining power to normal is 0.5 gm. of $NaHCO_3$ per kilogram of body weight. If the patient can swallow or a stomach tube is passed, sodium bicarbonate is just as effective this way as intravenously.

were not necessary since she was taking fluids well by mouth. Sufficient insulin was given daily to insure complete combustion of fats, since tests for diacetic acid and acetone in the urine were negative after the second day in the hospital. The patient, however, remained in coma and continued to have Kussmaul respirations after ketonuria had been abolished. On the 3d day she became markedly cyanotic and air hunger became very severe. A CO_2 combining power at this point was found to be 19 volumes %. Three grams of $NaHCO_3$ in a 7.5% solution were then given intravenously with most dramatic results. Cyanosis disappeared in 15 minutes. Respirations returned to a normal type. The patient became much brighter and was able to talk but was still stuporous. Through the day 4.5 gm. more of $NaHCO_3$ were given intravenously. As noted on the chart, the CO_2 combining power rose on that day to 45 volumes %.



The following day she was found in the same state of collapse and the CO_2 combining power was 22 volumes %. The same dramatic response followed intravenous administration of 3 gm. of $NaHCO_3$. Since the patient could now take fluids by mouth, she was given 1000 cc. of a 5% solution $NaHCO_3$ (50 gm.) orally over the next 12-hour period. The CO_2 combining power rose to 82 volumes % and gradually came down to the normal level of 55 volumes % by the 12th day. She was able to converse and was improved in all respects. As noted on the chart, the N.P.N. and blood sugar responded satisfactorily. From the 5th day on, the patient was given a diet of milk and cream containing 2000 calories and 100 gm. of available glucose.

This case serves to illustrate the rapid clinical and chemical improvement that may be brought about in a moribund patient when alkali therapy is added to the usual treatment of diabetic coma.

While it is not implied that alkali is necessary in every case of diabetic coma, its routine administration will replace a certain amount of the base which has necessarily been rendered unavailable.

However, in a small group of cases in which the acidosis is severe and the coma has been prolonged, the administration of sodium bicarbonate may be and sometimes certainly is a life-saving measure.

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THE VISCOSITY, PROTEINS AND LIPIDS OF THE BLOOD PLASMA IN ESSENTIAL HYPERTENSION.

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Many studies have been reported of the viscosity of the blood in hypertensive states, the great majority of the observations having been made upon whole blood. These investigations have demonstrated no consistent relationship between blood viscosity and the presence or degree of hypertension. Since the viscosity of whole blood is influenced by that of the plasma as well as by the number and volume of red blood cells,[1] the conflicting reports may be due, on theoretical grounds at least, to the almost universal failure to take into consideration possible variations in plasma viscosity. Indeed, recent studies[1,2] suggest that this factor alone

may be of importance in influencing the level of arterial blood pressure. Certainly, variations in blood viscosity, in the presence of identical hematocrit values, may be dependent upon differences in plasma viscosity. On this basis, the observation, by Harris and McLaughlin,[3] of increased blood viscosity in 35 of 40 hypertensive individuals with normal hematocrit values might be interpreted as being dependent upon increased plasma viscosity.

The present study was undertaken for the purpose of investigating the viscosity of the blood plasma in essential hypertension and its relation to certain factors that may influence it. By far the most important of these are the plasma proteins; it is, indeed, questionable whether any other factor is of practical significance in this connection under conditions compatible with life. Plasma lipid determinations were made because of the theoretically possible effect of these substances upon viscosity, as suggested by Fishberg.[4]

Material and Methods. Determinations were made upon 23 samples of blood obtained in the postabsorptive period from 21 patients with essential hypertension, with and without evidence of renal functional impairment. In addition, similar studies were made in 9 normal individuals and in 7 other patients for purposes of comparison. Heparinized plasma was employed for the viscosity and protein determinations and oxalate plasma for the lipid estimations. Plasma viscosity was measured by a concentric cylinder method[1] with the substitution of a more delicate torsion wire in order to increase the sensitivity of the apparatus for use with plasma. All viscosity values are recorded as relative to water at 37° C. The plasma protein fractions were separated by the method of Howe,[5] employing appropriate concentrations of sodium sulphate, buffered according to the suggestion of Medes;[6] fibrinogen and globulin were determined by difference. Digestion was accomplished by phosphoric-sulphuric acid mixture and potassium persulphate,[7] and the nitrogen was determined by distillation and titration. All determinations were performed in duplicate. Fatty acids were determined by the oxidation method of Bloor,[8] cholesterol by the method of Myers and Wardell[9] and lipid phosphorus by the method of Youngburg.[10]

Observations and Discussion. The values for the various plasma protein fractions and plasma viscosity in 9 normal individuals are presented in Table 1. The protein values are in close agreement with those reported by other investigators[11,12] who employed the same methods. The viscosity values for normal heparinized plasma, ranging from 1.76 to 1.99, averaging 1.88, are somewhat higher than those previously reported for oxalate plasma.[1]

The data obtained in the group of 21 patients with essential hypertension are presented in detail in Table 2. The total protein concentration, ranging from 5.61 to 8.66 gm. per 100 cc., shows a distinct tendency to vary within the high normal range, the average

of 7.45 being raised to 7.54% if the last case (D. Mc.), with a rather advanced grade of renal functional insufficiency, be excluded from the calculation. Govaerts[13] believed that the plasma protein concentration, as well as the osmotic pressure per gram of protein, was increased in essential and in nephritic hypertension. On the other hand, Moore and Van Slyke[14] could demonstrate no consistent relationship between the concentration of plasma proteins and the degree of elevation of blood pressure in patients with nephritis. The plasma globulin values in this series are within the normal range, but those for fibrinogen (0.16 to 1.18, averaging 0.5 gm. per 100 cc.) and, in consequence, those for globulin plus fibrinogen (2.19 to 4.19, averaging 3.37 gm. per 100 cc.), are distinctly above normal. Fibrinogen values above 0.4 gm. were obtained in 11 of the 23 determinations in this group.

TABLE 1.—NORMAL INDIVIDUALS.

Case.	Viscosity.	Fibrinogen.	Globulin.	Fibr. + globulin.	Albumin.	Total protein.	NPN., mg. %
		Grams per 100 cc.					
♂ T. H.	1.90	0.29	2.28	2.57	4.61	7.18	28
♂ W. L.	1.76	0.21	2.24	2.45	4.45	6.90	30
♂ F. R.	1.89	0.26	2.49	2.75	4.62	7.38	29
♂ W. S.	1.88	0.28	2.99	3.27	3.61	6.88	32
♀ A. C.	1.88	0.16	3.42	3.58	3.45	7.03	31
♀ A. N.	1.82	0.22	3.01	3.23	4.60	7.83	29
♀ L. L.	1.94	0.17	2.44	2.61	4.80	7.41	32
♀ R. H.	1.99	0.32	2.77	3.09	4.22	7.31	21
♀ M. Y.	1.85	0.18	2.68	2.86	4.39	7.25	19
Average .	1.88	0.23	2.70	2.93	4.31	7.24	

The plasma viscosity values in the patients with essential hypertension range from 1.84 to 2.27 and the average, 2.01, is distinctly higher than the normal average (1.88). In only 1 instance (T. F., Table 2) was the viscosity below the average normal; a subsequent determination (11 weeks later) yielded a much higher figure. However, 10 values in this group are below the high normal figure (1.99), 13 being above the upper limit of normal. In view of these observations it would appear that previously reported high blood viscosity figures in hypertensive patients with normal hematocrit values may be due to increased plasma viscosity.

No attempt will be made here to review the literature dealing with the relationship between proteins and the viscosity of the plasma and serum; this has been done elsewhere.[15] The present data, as presented in Fig. 1, in which plasma viscosity is plotted against total plasma protein concentration, indicate that in normal

as well as abnormal plasma there is no consistently close relationship between these two factors. This is to be expected, since plasma, normal and abnormal, contains an undetermined number of protein fractions of variable concentration, each probably influencing the viscosity to a different degree. Unfortunately, despite the enormous amount of data available regarding the viscosity of several proteins under a variety of conditions, absolute values are not available for each of the plasma protein fractions under conditions prevailing in the plasma. However, it is generally recognized that fibrinogen has the highest and albumin the lowest vis-

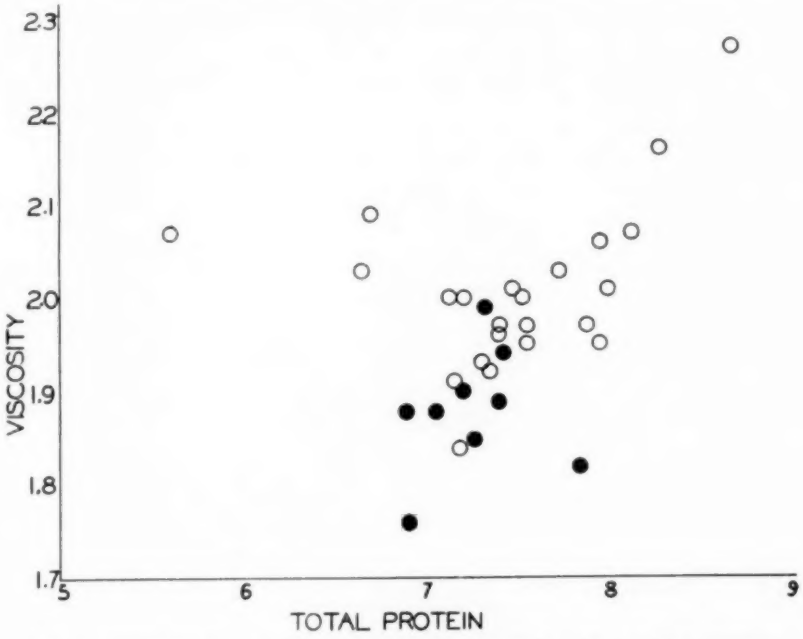

FIG. 1.—Viscosity plotted against total plasma protein. Open circles, cases of essential hypertension; solid circles, normal individuals.

cosity, the several globulin fractions occupying positions intermediate and transitional between these two.[16] As may be noted in Table 2, in many cases in the present series increased viscosity was associated with an increased fibrinogen or "globulin + fibrinogen" concentration; however, in a few instances, relatively low viscosity was associated with a high fibrinogen content, and *vice versa*.

The greatest divergence between plasma viscosity and total protein concentration occurs in those instances in which the albumin fraction is low. Since the effect of this protein upon plasma viscosity is relatively slight, normal values for the latter may be

obtained in spite of marked diminution in the former; indeed, in the presence of a simultaneous increase in globulins or fibrinogen, or both, as frequently happens, the plasma viscosity may be quite high. This is well illustrated in Case R. J., Table 3. This case, as well as others in this series, also indicates the apparent lack of influence of plasma lipids upon plasma viscosity. Fishberg[4] believed that an increased cholesterol content tends to diminish viscosity by favoring a water-in-oil type of emulsion. The fatty acids were slightly above normal in many cases in the hypertensive group, the average concentration, 465 mg. per 100 cc., being considerably higher than the average value, 353 mg., obtained by Boyd[17] in normal individuals. This factor, however, bore no demonstrable relation to the plasma viscosity, as indicated by Case M. M., in Table 3, with an extremely high fatty acid concentration and relatively low viscosity, in spite of a rather high fibrinogen content. We believe that, under conditions ordinarily existing in the blood, the plasma viscosity is practically unaffected by changes in factors other than the plasma proteins, particularly fibrinogen and globulin. In our opinion, the discrepancies which apparently exist between viscosity and protein concentrations would be eliminated if the individual viscosities and concentrations of the several globulin fractions were known.

There was no consistent relationship between plasma viscosity and either systolic or diastolic blood pressure in the present series. Two normal cases presented higher viscosity values than several in the hypertensive group; moreover, an increased viscosity may accompany acute infectious processes with an associated increase in plasma fibrinogen and, at times, globulin, as in Case E. R., Table 3, with no rise in blood pressure. It would appear unlikely, therefore, that increased plasma viscosity is of fundamental importance in the pathogenesis of hypertension. However, it may be possible that vascular hypertension is in part dependent upon changes incident to the effects of increased plasma viscosity persisting over long periods of time.

Summary. 1. The total plasma protein concentration in a group of 21 patients with essential hypertension was within practically normal limits, the average being somewhat higher than the average normal. The albumin and globulin fractions were approximately normal but the fibrinogen concentration was considerably elevated in a large proportion of patients in this series.

2. The plasma viscosity was generally higher in essential hypertension than in normal individuals but values below the upper limit of normal were present in some instances. There was no demonstrable relationship between the plasma viscosity and the degree of hypertension.

3. The concentration of fatty acids was slightly above normal and the average considerably above the average normal. The plasma lipids appeared to bear no relation to the plasma viscosity.

TABLE 2.—ESSENTIAL HYPERTENSION.

Case.	Age.	Viscosity.	Plasma proteins. Fib.	Glob.	Fib. + glob.	Alb.	Total prot.	Plasma lipids. Cholesterol	Fatty acid.	Lipoid P.	NPN	Urea clear., %	Hb., %	R.B.C., millions	Urine. Alb.	Casts.	Sp. gr.	Eye-grounds.	Blood pressure.
			Grams per 100 cc.					Mg. per 100 cc.											
♂ J. B.	40	1.97	..	..	3.70	4.17	7.87	147	468	7.1	28	153	92	4.75	0	0	1.028	+	195/120
♀ A. W.	50	2.03	0.16	2.44	2.60	4.04	6.64	..	..	..	37	105	78	4.05	++	0	1.034	+++	200/140
♀ A. N.	55	1.97	0.72	2.33	3.05	4.34	7.39	159	412	7.3	29	98	85	4.00	0	0	1.020	0	220/120
♀ C. T.	40	2.07	0.65	3.37	4.02	4.09	8.11	160	462	8.2	32	84	90	4.60	0	0	1.035	+	180/110
♂ *W. J.	53	2.16	0.42	3.26	3.68	4.59	8.27	256	524	6.8	49	78	100	5.30	+++	+	1.016	++	220/140
		2.27	0.87	3.32	4.19	4.47	8.66				49								
♀ M. S.	54	1.91	0.39	2.88	3.27	3.87	7.14	293	586	7.1	32	73	90	5.25	0	0	1.022	+	180/100
♂ B. B.	45	1.95	0.36	3.04	3.40	4.14	7.54	235	425	6.9	25	68	88	4.60	0	0	1.026	..	190/110
♀ B. L.	55	1.96	0.24	2.72	2.96	4.42	7.38	186	472	6.8	23	68	90	4.90	0	0	1.026	0	206/100
♀ J. C.	44	2.01	0.83	3.23	4.06	3.92	7.98	183	427	8.7	25	66	83	4.20	0	0	1.016	+	190/110
♀ E. G.	48	2.06	0.77	3.31	4.08	3.81	7.89	140	490	7.6	26	66	86	4.10	0	0	1.024	+	200/110
♂ L. W.	66	2.03	0.30	3.04	3.34	4.38	7.72	176	442	6.4	29	62	88	4.60	0	0	1.026	++++	210/110
♀ M. D.	27	1.95	..	..	3.58	4.36	7.94	113	432	6.7	25	61	67	3.50	0	0	1.030	0	185/120
♂ H. W.	64	1.93	0.66	2.19	2.85	4.44	7.29	210	465	7.2	37	55	80	4.10	0	0	1.021	+	190/110
♀ F. Y.	40	2.00	1.18	2.67	3.85	3.67	7.52	206	426	9.1	30	54	92	4.50	0	0	1.022	+	180/115
♀ M. P.	34	2.01	0.27	2.44	2.71	4.76	7.47	180	416	7.4	30	53	82	4.20	0	0	1.030	+	185/115
♀ J. Mc.	53	1.97	0.38	2.71	3.09	4.45	7.54	283	570	7.8	27	48	85	4.10	0	0	1.020	+	210/120
♀ S. W.	39	2.09	0.18	2.72	2.90	3.78	6.68	..	..	..	21	40	77	5.50	+	0	1.021	+++	200/120
♂ †T. F.	63	1.84	0.28	2.75	3.03	4.14	7.17	138	432	6.4	41	39	95	4.10	0	0	1.020	++	220/120
		2.00	0.32	2.66	2.98	4.21	7.19												
♀ L. P.	54	1.92	0.41	2.69	3.10	4.24	7.34	184	..	..	30	32	100	5.10	++	0	1.022	+	170/100
♀ A. C.	53	2.00	0.45	3.26	3.71	3.40	7.11	286	..	..	38	31	94	5.10	++++	+	1.012	+	220/105
♂ D. Mc.	50	2.07	0.74	2.69	3.43	2.18	5.61	158	..	..	47	22	72	3.60	++++	+	1.024	+++	170/115
Average	..	2.01	0.50	2.84	3.37	4.08	7.45									0			

* (1) March 13, 1935. (2) April 30, 1935.

† (1) March 6, 1935. (2) May 28, 1935.

TABLE 3.—Miscellaneous Conditions.

Case.	Age.	Condition.	Viscosity.	Plasma proteins. Fib.	Glob.	Fib. + glob.	Alb.	Total prot.	Plasma lipids. Cholesterol	Fatty acid.	Lipoid P.	NPN.	Urea clear., %	Hb., %	R.B.C., millions.	Blood pressure.
				Grams per 100 cc.					Mg. per 100 cc.							
♀ M. M.	18	Subsiding, acute	1.90	0.67	2.47	3.14	1.68	4.82	726	1264	12.8	39	29	80	4.3	140/100
♀ F. T.	33	Chronic nephritis	1.77	0.14	2.61	2.75	3.36	6.11	..	..	..	46	48	50	3.0	170/110
♂ G. P.	23	Chronic nephritis	1.75	0.11	2.23	2.34	4.23	6.57	..	..	..	27	68	87	4.5	170/120
♂ R. J.	13	Lipoid nephrosis	2.13	0.61	2.69	3.30	1.07	4.37	642	1014	9.3	24	88	74	4.2	116/92
♀ T. S.	34	Convalescent toxemia of preg.	1.96	0.17	2.86	3.03	1.76	4.79	248	..	..	22	..	74	4.1	150/90
♂ E. R.	32	Acute gonococcus arthritis	2.20	0.67	3.56	4.18	3.50	7.68	..	..	..	31	..	88	4.8	120/90
♂ J. F.	47	Prostatism	1.91	..	..	3.29	3.98	7.27	..	..	..	110	..	68	3.7	136/94

4. The relationship between the various plasma proteins and plasma viscosity may perhaps be more clearly established when the concentrations and relative viscosities of the several globulin fractions can be determined accurately.

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THE USE OF CALCIUM GLUCONATE AS A CIRCULATION TIME TEST.*†

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The need of more satisfactory objective methods of estimating cardiac function is too obvious to require comment. Exercise tolerance tests and vital capacity determinations are of limited

* Calglucon, 20%, used in this study, was made available through the courtesy of the Sandoz Chemical Works, Inc.

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usefulness, and venous pressure measurements afford no direct information as to the state of the pulmonary circulation.

The volume of blood pumped by the heart each minute is conveniently spoken of as the "cardiac output," and is for practical purposes the most satisfactory criterion of its functional efficiency. Determination of the cardiac output, however, is difficult, and only recently have methods been developed which give accurate results.[1] The velocity of the blood flow, however, may easily be determined with a fair degree of accuracy, and represents in considerable measure the effect of cardiac work and cardiac strain.

Many methods have been proposed for estimating the speed of the circulation, the majority of which depends upon the injection of a foreign substance into the circulation at one point and detecting its arrival at another by means of a signal or end reaction. The term "circulation time" denotes the interval of time necessary for

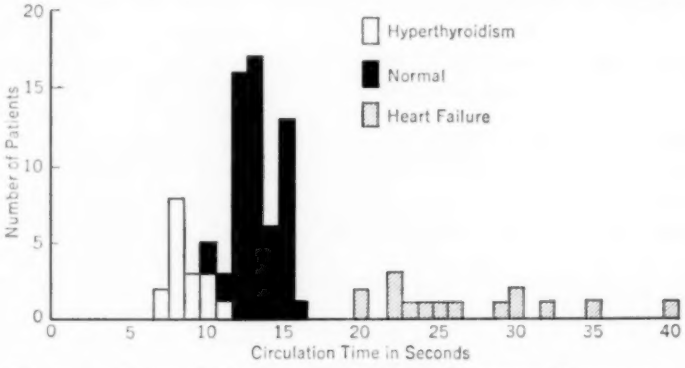

CHART 1.—CHART OF CIRCULATION TIMES IN DIFFERENT CONDITIONS.

the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection.[2] Thus, the interval elapsing from the moment of injection of a bitter substance into an antecubital vein and its perception on arrival in the tongue is spoken of as the "arm to tongue circulation time," and necessarily includes the blood flow through the lungs, which is the major portion of the path.

Robb and Weiss[3] and Blumgart and Yens[4] have each proposed criteria which should be met by the ideal procedure for determining circulation time. The substance must be non-toxic in the amounts utilized; it should itself not affect the rate of blood flow; the reaction time after arrival in the end organ should be short, and the signal should be clearcut; the effect should wear off quickly to allow of repeated measurements; and finally, it should be objective and, if possible, suitable for graphic registration.

Methods. Since the early experiments with fluorescein by Koch,[5] the following substances have at one time or another been employed

in determining the speed of the circulation. An active radium deposit;[4, 6] histamin phosphate;[7] sodium dehydrocholate;[8] sodium cyanid;[3, 9] saccharin;[10] endoiodin, an organic iodin preparation;[11] calcium chlorid and calcium bromid;[12] volatile substances such as ether and perfumes for measuring the velocity on the arterial side of the pulmonary bed.[13]

Technical difficulties, expense, untoward or toxic effects, and the possibilities of venous thrombosis and local tissue damage are some of the objections that have at times been recognized in one or another procedure, in some instances by the proponent of the method himself.

Technique of Calcium Gluconate Test. A satisfactory method should be capable of being utilized by the practitioner at the bedside, employing the resources ordinarily at his command. The material should be readily available, free from toxic effect, and incapable of causing pain, thrombosis or tissue necrosis when rapidly injected. Such criteria are met by calcium gluconate, which in this country has become the preparation usually employed when intravenous or intramuscular calcium medication is indicated. The patient reclines, with the arm at the level of the right auricle. After entering the vein, the tourniquet is withdrawn, and the circulation is permitted to return to normal. A stopwatch is held in the left hand, and 3 to 5 cc. of the 10% solution is injected as rapidly as possible with the other, through an 18-gauge needle. When the larger amount is used, a characteristic response is invariably elicited. The time required for completing the injection is subtracted from the total circulation time, although if a needle of large bore be used, this rarely occupies more than ½ second. There has been recently made available a 20% solution of calcium gluconate which permits the use of smaller volumes, and minimizes the factor of injection time. Recent tests have been carried out with 2.5 cc. of this solution with improved results. There is no pain, thrombosis or slough should the injection be improperly made. The patient announces the onset of the hot sensation in the pharynx by crying out "hot," or some other such signal. The sensation is sudden in onset, and wells up rapidly into the throat very much like a "gust of steam," to use the expression of one patient. It is next felt in the face, and then successively in the anterior chest, perineum, the hands, and finally the feet. These effects depend upon the arrival of the solution in the respective peripheral arterial beds. The onset of the sensation in the throat and tongue is most intense, as the substance is here present in greatest concentration.

After the sensation has entirely subsided, usually within 1 or 2 minutes, the reading may be repeated, without removing the needle from the vein. The second reading usually checks closely with the first, indicating that the first injection of the material has no great effect on the circulation itself. No discomfort is experienced by

the patient as a result of the rapid injection, even in those with advanced heart failure. One patient with auricular fibrillation and severe heart failure of rheumatic origin complained of palpitation shortly after the test, but this was the only instance observed. We have tested a number of patients who were under digitalis medication and have observed no instance of untoward calcium and digitalis synergism. This method has the additional advantage that circulation time readings to the extremities may be made, if desired, affording a possible approach to the study of peripheral vascular disease. However, it is entirely subjective and cannot be carried out without the coöperation of the patient.

Most of our patients were at rest in bed in the hospital, some were dispensary patients, and others were seen at home or in the office. We have not found it necessary to perform the test under basal conditions, as advocated by some, inasmuch as Boothby and Rynearson[14] have shown that the increase in cardiac output in hyperthyroidism is greater than that observed when the metabolism of normal subjects is raised to a corresponding level by exercise. They conclude that there is an additional factor in hyperthyroidism which stimulates the circulation beyond that required by the metabolic demands of the tissues. Furthermore, Rosenblum states that when the level of metabolism is raised by dinitrophenol,[15] the circulation speed is not increased as it is with the administration of thyroid substance or in spontaneous hyperthyroidism.

Results. Duplicate readings were made on 156 patients. In those with cardiac failure, as many as 6 or 8 duplicate tests were made at various times during their illness, and recovery of compensation was always associated with a shortening in circulation time. The results are shown in Table 1.

TABLE 1.—CIRCULATION TIME DETERMINATION IN 156 PATIENTS.

Condition.	No. of patients.	Reading in seconds.			Probable error.
		Lowest.	Highest.	Mean.	
Normal	60	10	16	12.5	±1.0
Hyperthyroidism	17	7	11	9.9	±1.1
Cardiac failure	15	20	40	26.7	±3.8
Myocardial insufficiency	11	16	23	18.7	
Bronchial asthma	4	12	14	13.0	
Nephritis with and without edema	2	13	13	13.0	
Compensated valvular heart disease	8	11	14	13.0	
Hypertension	25	8	16	12.0	±1.4
Fever	7	8	13	10.0	
Anemia	3	8	11	9.0	
Myxedema and hypothyroidism	4	19	22	20.0	

The group of 11 patients designated "myocardial insufficiency" were not decompensated, but in several there had been previous episodes of coronary thrombosis, and all showed electrocardiographic evidence of myocardial disease. There were no com-

plaints, except fatigue and dyspnea on exertion, and no physical signs of heart failure. One patient, in a severe attack of bronchial asthma, had a normal circulation time of 14 seconds. A woman with general anasarca caused by nephritis, showed a reading of 13 seconds. There were 8 patients with healed, compensated rheumatic valvular lesions who showed normal readings. Likewise, 25 patients with uncomplicated hypertension had circulation times from 8 to 16 seconds (average, 12).

In 21 patients, before or immediately after the tests with calcium gluconate, we carried out duplicate determinations with decholin. In these there was complete correspondence in 7 patients, a difference of less than 1 second in 9; less than 2 seconds in 1; less than 3 in 2, and a variation of 4 to 6 seconds in 2 other patients.

Summary and Conclusions. The arm to tongue circulation time, a relative index of the rate of blood flow through the lungs, is a useful test of the functional efficiency of the circulation. The velocity with which the blood flows through the lungs is a composite result of the oxygen demands of the body and the capacity of the heart and bloodvessels to propel the blood to meet such demands.

A simple method is described which lends itself to general use, and the results in 156 normal and pathologic cases are reported. The calcium gluconate method gives normal readings varying from 10 to 16 seconds, with an average arm to tongue circulation time of 12.5 seconds.

Hyperthyroidism increases the velocity of the blood flow, and cardiac failure markedly slows it. In myxedema and hypothyroidism there is a slowing of the circulation in proportion to the fall in metabolism. The test is helpful in the differentiation of edema of cardiac or renal origin, and may be of assistance in distinguishing between cardiac and bronchial asthma. The calcium gluconate test is approximately accurate, and easy to perform. No untoward effects have been observed, nor has there been any thrombosis or tissue damage in a single instance.

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THE EFFECT OF TWO WATER-INSOLUBLE SQUILL GLUCOSIDS UPON THE ELECTROCARDIOGRAM.

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Since the days of Withering[1] and his brilliant research upon foxglove in the treatment of dropsy, digitalis has overshadowed all the other drugs of this group in the treatment of cardiac edema. Squill, while consistently used for similar purposes, has occupied a position of secondary importance. The use of squill in medicine

dates back many centuries. Scheer and Sigerist,[2] in writing the history of squill, mention that Pythagoras and Galen recommended it to "prolong life," and describe its use by the early Egyptians and also the Romans.

The recognition that the members of this family of drugs are each composed of a number of glucosids has led to an immense amount of research for the purified glucosidal elements of both digitalis and squill. The processes for isolation and analysis of insoluble glucosids of squill were perfected by Dyas[3] and Ingersoll.[4]

Van Dyke and Wallace[5] investigated two of these squill glucosids in animals (scillonin A and B) and found they were less cumulative than ouabain, although the acute toxic effects produced by continuous intravenous injection were the same. Carr and Mayer[6] have recently reported favorable clinical experience with scillonin. They found that cardiac irregularity was a sign of intoxication as it is in digitalis. The Council on Pharmacy and Chemistry accepted the material last year.[7]

We have made a further evaluation of the cardioactivity of these glucosids in heart disease with congestive heart failure with electrocardiographic studies. Many serial electrocardiograms were taken on our patients before, during and after squill medication, giving a mobile picture of the effects of squill upon the electrocardiogram. With the renewal of interest in squill derivatives in the past few years we felt it worth while to report our findings of the electrocardiographic changes caused by this drug.

The effect of squill and its glucosids upon the electrocardiogram has not received a great deal of attention. In 1911, Turnbull[8] recorded the production of sinus arrhythmia, heart block, and "an irregularity whose nature cannot be decided with certainty but which may be a condition of heart alternation, or may be due to extrasystoles." One electrocardiogram taken in this study showed prolongation of the *P–R* interval from 0.16 to 0.3 second, and dropped ventricular beats.

In 1911, Windle[9] recorded partial and complete heart block in a patient as a result of digitalis, squill and strophanthus.

White, Balboni and Viko[10] (1920) reported on the "digitalis-like action of squill." They found that heart block was produced only by large doses of squill and that the *T* waves were flattened or inverted.

Kauffman[11] (1923) reported a series of cases of auricular fibrillation treated with digitalis and quinidin and squill and quinidin. He recorded the percentage of conversion to sinus mechanism as 41.3% with quinidin combined with digitalis. When squill and quinidin were used together he secured a higher percentage of 61.1%.

Boden and Neukirch[12] (1923) reported a patient with auricular flutter who regained a sinus mechanism under the influence of squill and relapsed to auricular flutter when the squill was discon-

tinued. They reported the electrocardiograms of warm-blooded animals showed extrasystoles, auriculoventricular block and ventricular standstill with continued beating of the auricles under the influence of squill.

Estabe[13] (1928) reported a patient with valvular disease in whom digitalis produced an auriculoventricular block. He changed the medication to squill because of its supposed non-cumulative action. Auriculoventricular block again resulted similar to that produced by the digitalis.

Van Dyke[5] (1933), in his studies of scillonin in cats and dogs, recorded an increased *P–R* interval, dropped beats, sinoauricular block and ventricular extrasystoles.

The effect of digitalis on the electrocardiogram has been more intensively studied with varied reports. The first records are credited to Cohn[11] and his coworkers in 1915. They reported the effects upon the *R–T*, *S–T* segments and *T* waves as present in 30 of 34 cases studied. They noted that the effect of the drug lasted in some cases as long as 22 days. Cohn mentioned several investigators who reported the effect of digitalis upon the electrocardiograms of animals in which the heights of the *T* waves were increased.

Pardee[15] (1920), in studying the rate of absorption of digitalis from the gastro-intestinal tract, reported: "The action of the heart muscle, as shown by the change in the *T* wave, begins between 2 to 4 hours after a dose of 1 minim of the tincture for each pound of weight . . . . diminution in its height, or a sinking of the level before the *T* . . . . which later results in an inversion of the *T* in one or more leads."

Pardee[16] (1923) in studying standardization methods of digitalis by its action on the human heart, stated: "This change in the *T* wave of the electrocardiogram comes on after small amounts of digitalis have been given by mouth, and increases steadily in degree as more of the drug is given."

Pardee,[17] in his book, states: "The effect of digitalis is very characteristic and usually consists of a diminution of the height of the *T* with a depression . . . . when right or left axis deviation is present the effect of the digitalis changes the *T* wave in such a way that it finally comes to be opposite in each lead to the direction of the predominant waves of the *Q–R–S*."

Brams[18] (1931) stated: "Electrocardiograms taken at frequent intervals over a long period of time failed to show a constantly lowered *T* wave. The *T* wave was never seen to be negative."

Coelho,[19] in studies on dog and human electrocardiograms, found only 18% showed changes in the *T* wave, disagreeing with American investigators.

A few reports of the clinical and electrocardiographic studies of squill, and the more comprehensive studies made with digitalis, would imply that the effects of the two drugs are somewhat the

same. The results of our studies with urginin* are in accord with these findings.

Method of Study. Twenty-five consecutive cases of heart disease with edema in the heart ward at the Cook County Infirmary were selected for study of the cardioactivity of urginin. The clinical diagnosis of these patients is appended in Table 1. All cases were in serious congestive heart failure with gross edema, with a functional classification of Group III, according to the standards of the American Heart Association.[20]

A number of these cases were of the coronary and syphilitic types of heart disease, where digitalis or squill may not have been the medication of choice. The patients were selected consecutively, however, on the basis of edema which did not recede with bed rest during the observation period.

Each case was carried through a control period of 5 to 20 days until evidence was established that bed rest was not effective in reduction of the edema. Electrocardiograms taken on alternate days during this period of observation gave evidence that there was no digitalis effect in the electrocardiograms. Only 3 cases, however, had received the drug within the 4 weeks prior to the observation period.

During the period of study of 5 to 20 days, the only medication given was liquid petrolatum, morphin sulphate and urginin. Fluid intake was not limited nor was salt restricted from the diet. Electrocardiograms with the conventional three leads were taken on alternate days and chest leads every fourth day. The patients were weighed daily at 7 A.M., their 24-hour daily fluid intake and urinary output were recorded and graphed. Apical and radial pulse rates were counted for 60-second periods at 8 A.M., 12 NOON, 4 P.M. and 8 P.M. and graphed.

A period of observation following the medication was made upon the majority of the patients and 5 cases were restudied with digitalis for comparison.

Dosage. Urginin was administered in tablet form once, twice or thrice daily after meals. Each tablet contained 0.5 mg. of the purified glucosid. The method of dosage varied in each individual, depending upon his response to the drug. Some patients received 3 mg., 6 tablets per day, for the first 2 to 4 days, followed by a reduction to 0.5 to 1.5 mg. for maintenance dosage. In others the original dosage was only 2 mg. with reduction to maintenance dosage later. A few patients were given daily doses of 1 to 1.5 mg. daily over a period of 10 to 40 days.

Results. *Ventricular Rate.* The ventricular rate was decreased in 21 of the 25 patients (84%). The decrease occurred in the patients with a normal sinus mechanism or auricular fibrillation. The 4 exceptions included 1 patient with chronic auricular flutter, 2 with uremia to which they succumbed, and 1 with a bronchopneumonia which caused his death. The decrease in the ventricular rate was most obvious in the group with auricular fibrillation and least marked in those with syphilitic heart disease.

Nineteen patients had a sinus mechanism, to whom urginin was administered from 7 to 32 days, with an average daily dose ranging from 1.3 to 2.22 mg.

* A mixture of equal parts scillonin A and scillonin B (Grisard-Dyas) accepted under the name "urginin" by the Council of Pharmacy and Chemistry of the American Medical Association.

TABLE 1.—CARDIAC DIAGNOSES.

Case No.	Etiologic	Anatomic	Physiologic
1	Thyrotoxicosis Thymoma	Occlusion of the superior vena cava Cardiac dilatation	Sinus mechanism.
2	Hypertension	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
3	Hypertension Arteriosclerosis Uremia	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
4	Arteriosclerosis	Myocardial fibrosis	Auricular fibrillation.
5	Arteriosclerosis	Coronary thrombosis Myocardial infarction Cardiac hypertrophy	Sinus mechanism. Extrasystoles (ventricular) Prolonged P–R interval.
6	Syphilis	Aortitic regurgitation Aortitis with dilatation Cardiac hypertrophy	Sinus mechanism.
7	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary thrombosis (old) Coronary sclerosis	Sinus mechanism.
8	Hypertension	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism. Extrasystoles (ventricular)
9	Pulmonary disease	Cor pulmonale	Sinus mechanism. Extrasystoles (ventricular)
10	Hypertension Arteriosclerosis	Cardiac hypertrophy	Sinus mechanism. Auricular flutter. Auricular fibrillation.
11	Thyrotoxicosis	No cardiac disease	Sinus mechanism.
12	Syphilis	Aortitis with dilatation	Sinus mechanism.
13	Syphilis Hypertension	Cardiac hypertrophy Aortitis	Sinus mechanism.
14	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary sclerosis	Auricular fibrillation. Sinus mechanism. Extrasystoles (ventricular)
15	Hypertension	Cardiac hypertrophy	Sinus mechanism.
16	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
17	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary sclerosis Coronary thrombosis	Complete A–V dissociation.
18	Hypertension Arteriosclerosis	Cardiac hypertrophy	Auricular fibrillation.
19	Hypertension	Cardiac hypertrophy	Auricular fibrillation.
20	Arteriosclerosis Hypertension	Coronary sclerosis Coronary thrombosis Cardiac hypertrophy	Left bundle-branch block with prolonged conduction time; A–V block.
21	Hypertension Arteriosclerosis	Coronary sclerosis Coronary thrombosis Cardiac hypertrophy	Left bundle-branch block. Partial auriculoventricular block.
22	Chronic bronchiectasis Chronic emphysema	Cor pulmonale	Sinus mechanism.
23	Arteriosclerosis Hypertension	Cardiac hypertrophy	Sinus mechanism.
24	Hypertension	Cardiac hypertrophy	Auricular fibrillation.
25	Arteriosclerosis Diabetes mellitus Hypertension	Coronary sclerosis Myocardial fibrosis	Sinus mechanism.

P Waves. No conclusions could be drawn concerning the effect upon the *P* waves. We found that the contour of the *P* waves varied mildly in the control studies. During the control and medication period, it was not uncommon to find slight changes in the contour of the auricular complexes, such as change in height, notch-

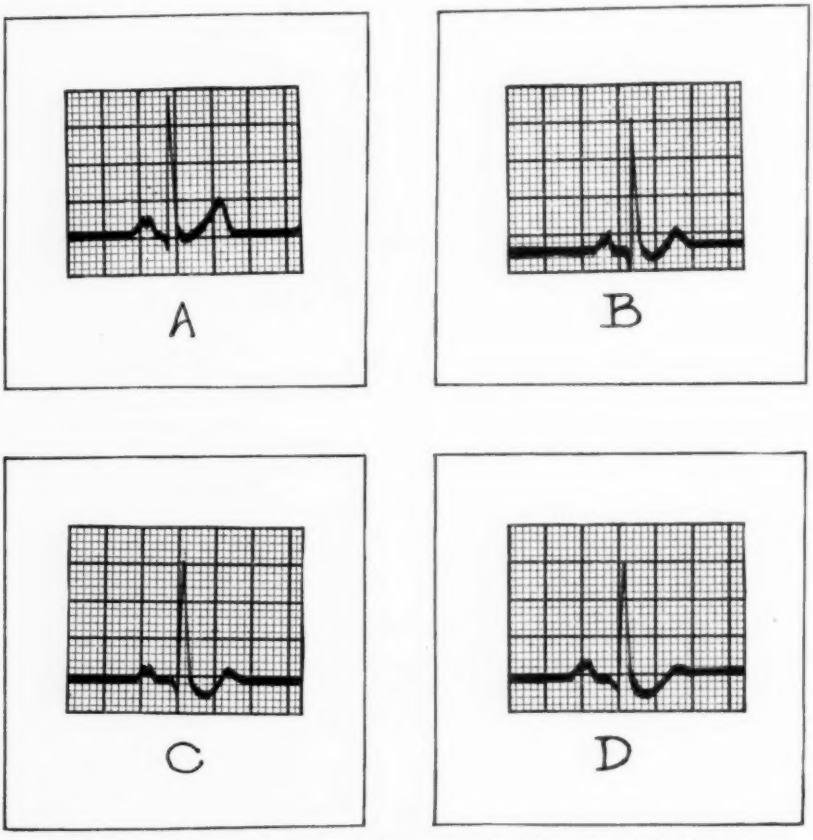

FIG. 1.—*A*, Control before medication. *B*, Slight depression of *R–T* segment and lowered *T* wave (5 days). *C*, Further depression of the *R–T* segment and lowered *T* wave (10 days). *D*, Concavity of *R–T* segment and almost total obliteration of *T* wave (15 days). Lead I throughout.

ing and widening. These changes were not sufficiently consistent, however, to warrant description of definite changes due to drug effect.

Effects Upon the P–R Interval. The *P–R* interval was prolonged in 16 of the 19 cases. Of the 3 patients whose electrocardiogram showed no change in the *P–R* interval, one received 23.5 mg. of urginin over a period of 18 days with an average dose of 1.3 mg.

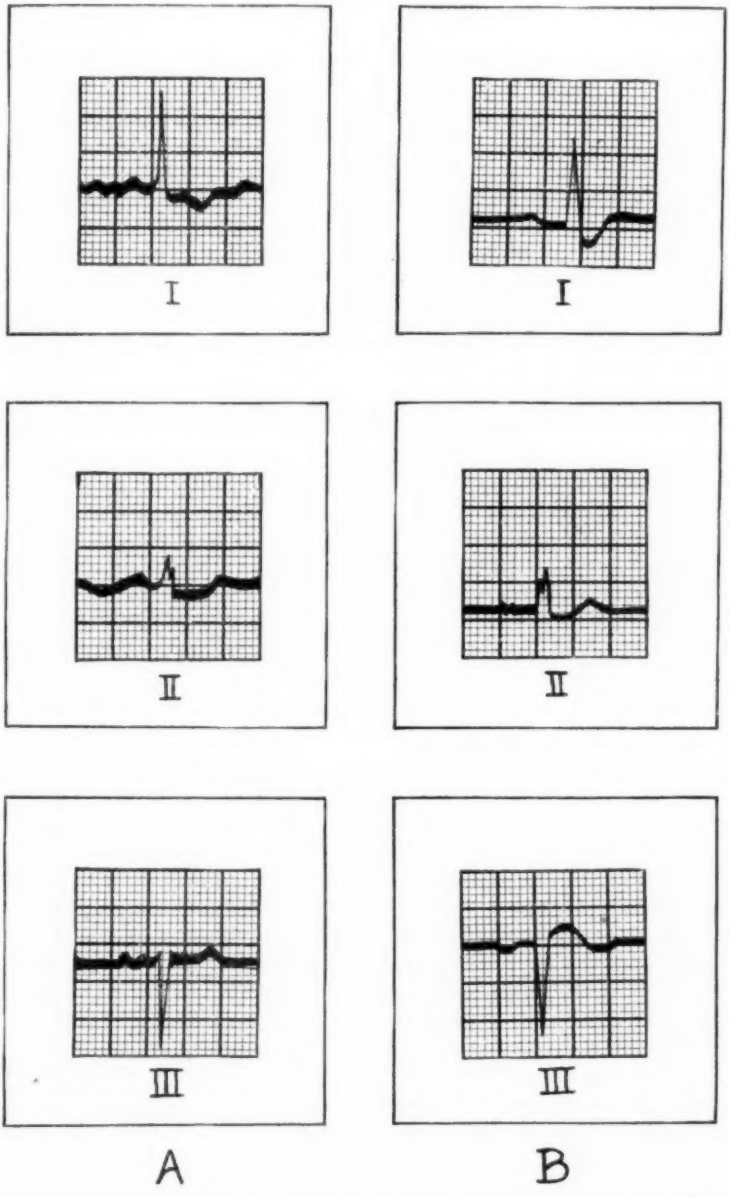

FIG. 2.—*A*, Electrocardiogram with left axis deviation before medication. *B*, Electrocardiogram with left axis deviation after 20 days of medication. (Total urginin intake, 30 mg.)

of urginin per day. The second received 61 mg. of urginin over a period of 32 days with an average daily dose of 2.21 mg. This patient was later checked with digitalis, receiving 51 grains of a known potent product over a period of 17 days with an average daily dose of 3 grains, without demonstrable change in a *P–R* interval of 0.2 second. All 3 of these patients showed characteristic changes in the *R–T* and *S–T* segments. Two were hypertensive vascular problems and 1 a case of syphilitic aortitis.

The minimal change recorded in the *P–R* interval was 0.02 second and the maximum increase was 0.12 (control, 0.16; medication period, 0.28). Prolongation of the *P–R* interval was not proportionate to the amount of drug administered. The patient who showed the maximum change of 0.12 second received only 14 mg. over a period of 7 days, or 2 mg. per day. Similar or greater dosage in other patients showed a lesser change.

Effect Upon the Q–R–S Complexes. No consistent changes were noted in the time interval of the *Q–R–S* complexes. The height sometimes varied but this appeared to be consistent with increase or decrease of edema. The descending limb of the *R* spike projected below the base line as described in the next paragraph with changes in the *R–T* segment. Similarly the ascending limb of the *S* wave in Lead III projected above the base line as the *S–T* segment was changed.

One series of electrocardiograms showed a prominent *Q* wave in Lead III, which became shorter under medication and longer after the drug was discontinued.

Effect Upon the R–T and S–T Segments. The *R–T* or *S–T* segment was affected in all 25 cases. With a dosage of 1 to 3 mg. per day, this change was usually noted on the fourth or fifth day of medication. In those cases with the *Q–R–S* complex directed upward in all leads, the isoelectric *R–T* segment became concave, with mild blunting of the peak of the *T* wave when it was directed upward. With continued administration of the drug, the concavity deepened and the descending limb of the *R* spike progressed below the base line, while the *T* wave became obliterated. These changes were present in all leads, usually most marked in Leads II and III.

In those cases with diphasic or inverted *T* waves the *R–T* segment was sometimes directed diagonally or showed a convex curve. The effect of urginin on these segments was similar in that they assumed the same concave appearance as that described above, although the descent of the descending limb of the *R* wave below the isoelectric level was less marked.

In cases with left axis deviation with the *T* wave directed upward in Lead III, the change in the *S–T* segment consisted of a convexity with deformity of the *T* wave. The ascending limb of the *S* spike progressed above the base line.

T-wave Effects. The contour of the *T* wave was affected in all

cases but this appeared to be a part of the change in the *R–T* or *S–T* segment. No case showed straight inversion of the *T* waves in any lead.

Auricular Fibrillation. Four cases of auricular fibrillation were studied. The ventricular rate was slowed in all cases. The *R–T* and *S–T* segment changes as just described appeared in all 4 cases.

Heart Block. One case with complete *A–V* dissociation, presumably due to coronary thrombosis, was given urginin. The mechanism changed to a sinus mechanism with a prolonged *P–R* interval. The change was considered a coincidence.

There were 2 cases of left bundle-branch block in the series. The urginin showed no effect upon the contour of the *Q–R–S* complexes but the *R–T* and *S–T* segments became concave and convex in all leads. In 1 patient with bundle-branch block the mechanism changed to auricular fibrillation, with left axis deviation, and with the *T* waves in the same direction as the main deflections. The *Q–R–S* complex originally measuring 0.16 second was changed to measure 0.12 second with disappearance of the notching. Eight days after cessation of the medication the sinus mechanism was resumed with characteristic left bundle-branch block. Repetition of the drug in lesser amounts failed to reproduce this phenomenon.

Auricular Flutter. One case of the series had a chronic auricular flutter. Previous to the study the patient had been treated with quinidin, digitalis and a combination of both without results. During the urginin medication short periods of auricular fibrillation were observed. Paroxysmal periods of sinus mechanism then occurred and the patient eventually resumed a permanent sinus mechanism.

Production of Cardiac Irregularity. In 12 of the 25 cases, extrasystoles were noted. The origin was ventricular in 5 instances, both ventricular and auricular in 4, ventricular and nodal in 2, and nodal alone once. Three of these patients showed extrasystoles both before and during the medication periods. Nausea was observed in only 2 of the 25 cases as an indication of overdosage.

Five cases developed auricular fibrillation during the period of medication. One case (formerly converted from auricular fibrillation to a sinus mechanism with quinidin sulphate) reverted to auricular fibrillation under urginin without quinidin. A second case developed auricular fibrillation on the second day after the onset of bronchopneumonia and the arrhythmia persisted until death on the fourth day. A third case developed auricular fibrillation on the fifth day of medication receiving 3 mg. per day, sinus mechanism was resumed in 48 hours. This patient receiving digitalis (3 grains per day) developed auricular fibrillation at the end of 7 days (total, 21 grains). Cessation of the drug was followed by resumption of a normal sinus mechanism. This phenomenon was repeated on 4 occasions with digitalis. One patient developed

auricular fibrillation on the third day of medication after receiving 9 mg. of urginin (3 mg. per day). The medication was stopped for 3 days and again resumed for a period of 7 days at the same dosage. At the end of another 7 days, sinus mechanism was resumed. The patient was later given 2 mg. per day without change in mechanism. One patient developed auricular fibrillation after 12 days with a dose of 2 mg. per day. This patient had a complicating bronchopneumonia.

Summary. The effects of squill glucosids upon the electrocardiogram appeared to be characteristic and fairly consistent, particularly upon the R–T and S–T segments. The recorded changes of concavity and convexity produced were similar to those produced by digitalis as reported by Cohn and Pardee. In those patients whom we studied with both urginin and digitalis the changes produced were similar with equivalent amounts of each drug over equal periods of time.

There was a wide variation in the degree of effect produced in different patients, implying a variable amount of absorption of the ingested drug, a difference in the response of the patient, or other unknown factors.

In therapeutic doses, which is a relative term varying with each patient, the effects of urginin, like those of digitalis, appeared to be limited to an effect upon the R–T or S–T segment, slight prolongation of the P–R interval and occasional extrasystoles.

In patients intolerant to the medication, the effects of overdosage appeared to be the production of frequent extrasystoles, marked prolongation of the P–R interval and the production of auricular fibrillation.

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THE RÔLE OF THE LABORATORY IN THE DIAGNOSIS OF GALL BLADDER DISEASE.

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In the diagnosis of gall bladder disease the laboratory has come to be of inestimable help and often takes precedence over the history and physical findings in confirming or denying the opinion. The mimicry of the gall bladder picture by extrabiliary tract conditions has long been recognized. Yet, the very recent statement by Graham and Mackey,[1] that "it is perhaps not sufficiently appreciated that many conditions are often confused with gall bladder disease," reiterates the need for a highly critical attitude on the part of the diagnostician and a thorough investigation of every patient suspected of having gall bladder disease, in order that the operations unwisely performed upon the biliary tract may be avoided.

It was thought that it might be of interest to study a group of patients suspected of having gall bladder disease, in which duodenal drainage was uniformly performed and interpreted, in order to determine to what extent the results of such investigation could be relied upon. To this end, non-surgical biliary drainage was in all cases performed by one of us (H. S.). Microscopic examination of the bile so obtained was made by the same individual and an opinion of the biliary tract findings rendered independently of the historical data and without knowledge of the Roentgen ray report. A single drainage only was done in each patient. Very careful roentgenologic technique and expert roentgenologic opinion were

available for each case, although the Roentgen examination and the interpretation of the films were not done by the same individual. All patients were referred to Surgical Service E of our University Hospital, so that a uniform surgical opinion would be available. Of further interest is the fact that in 21 of the 30 cases in this series, the gall bladder bile obtained at operation was studied by a group thoroughly familiar with analytical bile chemistry, thus making the data available as a measuring rod for the pre-operative laboratory and the operative findings.

The usual pathologic examination was done on all cases in which the gall bladder was removed, even though the inadequacy of a pathologic examination in showing the degree of disordered function, or even to assure its presence, is well known. Graham and Mackey[1] recently indicated the precise value of this examination in establishing the status of the removed gall bladder. "The surgeon, if he finds little evidence of a pathologic change at the operation, is likely to find solace and justification in the microscopic examination of the organ. Unfortunately, however, this examination is unlikely to be of much help in just those cases in which the help is most needed. It is well known, for example, that there is practically no agreement among pathologists as to what constitutes a normal gall bladder. It is rare, therefore, for a gall bladder to be pronounced normal on the basis of a microscopic examination."

For the diagnosis of inflammatory disease of the gall bladder, gastroenterologist and roentgenologist both rely upon recognizable changes in the same two functions of the organ, its ability to absorb water and its ability to empty its contents. The gastroenterologist's definition of normal gall bladder function depends upon his ability to obtain an adequate gall bladder fraction of bile, of proper concentration, after inducing duodenal relaxation.*

The Roentgen interpretation of normality depends for its success upon concentration of the dye and upon the changes in the size of the shadow as a result of emptying subsequent to the administration of a fat meal. The biliary drainage studies depend in part upon the ability to obtain a gall bladder fraction. When this is obtainable the experienced investigator should be able, as a rule, to indicate derangement of function with as much certitude as can the roentgenologist from a cholecystogram.

In the bile obtained by non-surgical biliary drainage, an alteration of the gall bladder function will be reflected in an inadequate amount of "B" bile, in an imperfectly concentrated "B" fraction, or in a complete absence of a "B" fraction. This last may be indicative not only of abnormal function, but also of cystic duct occlu-

* An adequate "B" fraction (of Lyon) consists of 30 to 50 cc. of dark brown, black brown, or green black bile, showing in the drainage collected a clearly marked difference from the fraction obtained before the so-called "duodenal stimulation" and followed again by a lighter portion.

sion or of a functioning or abnormally functioning gall bladder filled with stones.

In 1923, Hollander[8] reported cholesterol crystals in gall bladder bile in cholelithiasis. This was confirmed by Mateer and Henderson,[9] Einhorn[10] and Jones.[11] The latter 2 reported cases in which bilirubin calcium pigment, in addition, had been found in the duodenal aspirate. In 1928, Piersol, Bockus and Shay[7] stressed the significance of these microscopic findings in the bile in gall stone disease. Further experience in a series previously reported,[12] and in this group of patients, has fortified the confidence placed in the finding of cholesterol crystals and characteristic pigment in bile obtained by the Lyon method of non-surgical biliary drainage. Briefly, the presence of both cholesterol crystals and supposed calcium bilirubinate in drainage bile, in our experience, has been invariably associated with the presence of gall stones. The finding of one of these elements alone strongly indicates the presence of stones. When only cholesterol crystals are found, cholesterosis without stones will occasionally be discovered at operation. When the pigment alone is present, the diagnosis of stones must be more cautiously considered, particularly if jaundice is, or recently has been, present. The absence of these elements in the bile when no "B" fraction is obtained, makes it impossible by drainage alone to determine the presence or absence of stones. In such instances stones may be present, but due either to cystic duct occlusion or the failure of the gall bladder to empty, no evidence of their presence may be found in the drainage bile.

Rafsky[13] recently suggested that the importance of these microscopic findings lies in their quantity. However, we believe that the certain identification of a few cholesterol crystals and minute amount of the characteristic pigment is as significant as the findings of large quantities of each.

This report is based upon the data obtained in patients with gall bladder disease, all of whom came to operation. In Chart I are given the findings as reported from gall bladder drainage and cholecystography.

CHART I.—DIAGNOSIS OF STONES BASED ON THE ROENTGEN AND DRAINAGE FINDINGS: STONES PRESENT 21, STONES ABSENT 9.
PRE-OPERATIVE DIAGNOSIS.

Roentgen ray.	Bile drainage.	Roentgen ray.	Bile drainage.
10 stones	17	2* stones	1*
2 uncertain	3	7 no stones	8
9 no stones	1		

* A case in which pigment alone was found in the drainage following a severe attack of biliary colic.

The advantage of microscopic study of biliary drainage fluid, over cholecystography in the diagnosis of stones lies in the fact that the experienced microscopist can find definitely formed elements which

even in minute quantities indicate the presence of calculi, while the roentgenologist is dependent upon a contrast in shadows in the gall bladder area. Obviously, the Roentgen criteria are subject to more disturbing variables than the microscopic ones. We do not wish to imply that by non-surgical drainage stones are invariably diagnosed. One case (S. T.) in the series, which did yield a small but definite "B" fraction, failed to show either crystals or pigment in the bile, yet stones were found at operation. Like many other laboratory tests a positive result may be accepted with greater certainty than a negative one. Persistence and care are required even by the very experienced microscopist. Examination of the sediment after centrifugalization should always be made before the specimen is to be considered negative and it is of great importance that the material be examined shortly after it is obtained.

Diagnostic drainage is of value in cases of common duct stone after cholecystectomy. We[2] have previously recorded such a case and in this series there is another such instance.

Case Abstract. I. C., female, aged 55, had a cholecystectomy in 1927. Six years later she suffered a recurrence of attacks of epigastric pain, nausea and vomiting. There was no jaundice. Cholecystography did not yield any additional information. In the bile obtained by non-surgical drainage numerous clumps of typical pigment were found. In the absence of jaundice, a diagnosis of stone in the duct could be made from this finding in the bile. At operation, a bullet-shaped black stone was found in the common duct measuring about 1 cm. in length and 0.5 cm. in diameter.

Of particular interest in this series has been the availability of the chemical data obtained by the analysis of the bile removed from the gall bladder at operation. As a result of the studies by Ravdin, Johnston, Riegel and Morrison,[3–6] on the fate of the various liver bile constituents in the healthy and diseased gall bladders, criteria are at hand by which the disturbed gall bladder physiology can be measured.

Ravdin[14] and his associates have studied in detail the changes produced in the normal gall bladder in the bile constituents brought to it from the liver and have shown how the various stages of gall bladder disease effect these changes. While significant alterations may be produced in all the bile constituents, it was found that in general the concentration of chlorid and bile salts gives definite indication of the state of gall bladder function.

Compared with the chemical data obtained from an analysis of the gall bladder removed at operation, biliary drainage and cholecystography suffer equally in their attempt to measure gall bladder function. This analysis was made on 21 of the 30 cases in this series (Chart II). With a normally functioning gall bladder, chlorid is rapidly absorbed from the liver bile brought to the gall bladder, the mean concentration being about 10 milli-equivalents per liter. Bile salts, on the other hand, are concentrated, so that

normal gall bladder bile contains approximately 200 milli-equivalents per liter. Damage to the gall bladder may result merely in a retardation of the rates of absorption and concentration, or, in severe damage, in an actual reversal of the normal process so the substances

CHART II.—THE COMPARISON OF CHOLECYSTOGRAPHY, BILE DRAINAGE, AND ANALYSES OF BILE OBTAINED AT OPERATION, WITH OPERATIVE FINDINGS.

Case.	Bile drainage.			Cholecystography.		Bile chemistry.		Operation.
	G. B. function.	Crystals.	Pigment.	G. B. function.	Stones.	M. eq/L Cl.	M. eq/L B. salts.	
F. P.	Cystic duct obs. non-funct.	—	—	Not stated	Pos.	126.8	None	Cyst. duct obs. stones
B. W.	Normal	Pos.	Pos.	Impaired	?	90.3	22.0	Black bile; stones.
F. G.	Non-function	Pos.	Pos.	Non-function	—	119.8	14.0	Stones.
R. A.	Partial	Pos.	Pos.	Partial	Pos.	No sample	51.0	Stones.
M. L.	Cystic duct obs. non-funct	—	—	?	—	134.2	Pink	Hydrops; stones.
F. S.	Non-function	—	Pos.	?	—	111.6	Yellow	Colorless B.; stones.
S. T.	Good	—	—	Partial	—	58.7	Faint blue	Black bile stones.
S. F.	Poor	Pos.	Pos.	Poor	Pos.	76.7	33.0	Distend.G. B.; stones.
M. B.	Poor	—	—	Normal	—	54.0	47.0	G. B. thickened.
M. Br.	Non-function	Pos.	Pos.	Partial	Pos.	37.5	27.0	Stones.
E. F.	Partial	Pos.	Pos.	Normal	Pos.	59.8	42.0	Stone.
P. K.	Poor	Pos.	—	Non-function	?	56.6	69.0	Stones.
T. S.	Non-function	Pos.	Pos.	Non-function	Pos.	44.8	23.0	Stones.
M. L.	Normal	Pos.	Pos.	Not stated	Pos.	53.3	2.0	Stones.
E. O.	Normal	Pos.	—	Normal	—	61.5	70.0	Dark bile; stones.
H. H.	Cystic duct obs. non-funct	—	—	Partial	Pos.	120.0	Faint blue	Hydrops; stone.
M. F.	Normal	—	—	Normal	—	No sample	Red	Dark bile; no stones.
M. S.	Poor	—	—	Poor	—	No sample	71.0	No stones.
L. W.	Non-function	—	Pos.	Non-function	—	No sample	Red	Stones.
M. A.	Normal	—	—	Partial	Pos.	41.0	134.0	No stones.
L. M.	Partial	—	—	Partial	—	115.9	7.0	No stones.

CHART III.—DATA OBTAINED WHERE DRAINAGE OR CHOLECYSTOGRAPHIC STUDIES INDICATED NORMAL FUNCTION.

Case.	Gall bladder function by bile chemistry.				Gall bladder bile at operation.
	Drainage.	Roentgen ray.	Chlorid.*	Bile salts.*	
B. W.	Normal	Impaired	90.3	22.0	Black bile; stones.
M. B.	Poor	Normal	54.0	47.0	G. B. thickened.
E. F.	Impaired	Normal	59.8	42.0	Stone.
M. L.	Normal	Not stated	53.3	2.0	Stones.
E. D.	Normal	Normal	61.5	70.0	Dark bile; stones.
M. F.	Normal	Normal	....	Red	Dark bile; no stones.
M. A.	Normal	Impaired	41.0	134	No stones.
S. T.	Good	Partial	58.7	Faint blue	Black bile; stones.

* Milli-equivalents per liter.

hitherto absorbed are poured into the bile, while substances that are normally concentrated are absorbed. These changes in the above two constituents result in an increasing concentration of chlorid and in a decreasing concentration of bile salts in progressive gall bladder disease. In all the gall bladder biles studied in this

series, there were definite evidences of gall bladder disease. In 13 of the 21, where the bile was studied by drainage a normal "B" fraction was not obtained and the cholecystographic studies also disclosed evidence of impaired concentration or emptying. But in 8 cases, drainage or cholecystography, or both, indicated a normally functioning gall bladder (Chart III). This is of interest because it shows the weakness of both methods in yielding criteria that definitely establish the normality of gall bladder function. The same criticism applies here as is directed at the attempt to measure liver function by a single functional test. The microscopy of the bile as obtained during drainage, has the advantage over the Roentgen ray, of permitting an examination of the bile crystallography and cellular débris. It would appear from a study of the chemistry of the gall bladder bile, that changes in concentration of the bile constituents may occur while the water-absorbing mechanism is sufficiently retained to produce adequate concentration of the dye in cholecystography, or concentration of the bile pigment to yield a so-called normal "B" fraction by drainage.

From a comparison of the non-surgical biliary drainage of Lyon and cholecystography, it has been our experience that the former is, as a rule, more effective in the diagnosis of gall stones. From the chemical data, it is obvious that a certain diagnosis of a normally functioning gall bladder can be had from neither procedure. One must remember that normal function of a gall bladder as measured by our present laboratory procedures pre-operatively does not preclude the presence of stones. In only 2 instances did both methods indicate a normal gall bladder. Patently, then, from the standpoint of the laboratory, a combined study of the bile, the result of non-surgical drainage and cholecystography, offers the most refined pre-operative diagnosis for gall bladder disease at present. Should it become possible to apply the data obtained from the chemistry of the recovered bile during non-surgical biliary drainage pre-operatively, we should then have the "open Sesame" to the diagnosis and understanding of gall bladder disease.

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THE EFFECT OF ERGOTAMIN TARTRATE ON NON-MIGRAINOUS HEADACHES.*

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Experience of the last few years has demonstrated that individual attacks of migraine headache can ordinarily be aborted by the use of ergotamin tartrate.[1] In the experience of two of us, the parenteral administration of the drug has stopped the initial headache treated in 90% of the patients.[2] In most of these patients headaches were severe and unaffected by the usual sedative drugs. The important question arises whether ergotamin tartrate is of specific value in migraine. If specific, an understanding of its action should shed light on the mechanism producing migraine headaches. If not specific, ergotamin tartrate should prove a headache panacea.

The literature is of little assistance. Trautmann[3] states that non-migrainous headaches are not helped by ergotamin but presents no detailed evidence. In this communication we present data which we have collected during the past 2 years.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation. The ergotamin tartrate (Gynergen) used was supplied by the Sandoz Company.

Materials and Methods. Our classification of migraine headaches has been a liberal one; recurring headaches with two or more of the satellite symptoms of hemicrania, family history, nausea and vomiting, visual aura, vasomotor symptoms, and failure of relief by ordinary means.

The non-migrainous headaches were those to be encountered on a neurologic service. Patients with psychoneurosis were excluded. Headaches were associated with the following conditions, namely, 8 patients with aseptic meningitis, of whom 7 had had subarachnoid injection of air, and 1 a subarachnoid hemorrhage; 6 patients with increased intracranial pressure, of whom 5 had brain tumor and 1 subdural hematoma; 7 patients with subnormal intracranial pressure following removal of spinal fluid; 8 patients with postconvulsive headache; 1 with sinusitis; 11 in whom the cause of the headache was not ascertained, and 5 in whom the headache was artificially induced by means of histamin phosphate injected intravenously. In the last named group the following procedure was used. Sufficient histamin to produce headache (0.1 to 0.2 cc. of a 1 to 1000 solution) was injected intravenously and the severity and duration (only a minute or two) of the resulting headache noted. After an interval of 20 or more minutes, ergotamin tartrate (0.25 to 0.5 mg.) was injected and 20 to 45 minutes later the previous dose of histamin was repeated.

Ergotamin tartrate was given to these patients in the same manner as to patients with migraine, namely, 0.5 mg. intravenously or subcutaneously. Besides the patient's statement of the effect on the pain, record was kept of the occurrence of nausea and vomiting, and of changes in blood pressure and pulse rate.

Results. The effect on the headache in these 46 patients, and comparison with the effect on the group of 120 migraine patients reported by two of us[2] was as follows:

	No. of patients.	Percentage with headache.		
		Stopped.	Unchanged.	Worse.
Non-migrainous patients	46	15	63	22
Migraine patients	120	89	8	3

There is thus a sharp contrast in the therapeutic effect in the two groups of patients. Ergotamin caused complete relief of headache in 89% of migraine patients and in only 15% of the other group; it made the existing headache worse in 3% of the migrainous and in 22% of the non-migrainous group. This difference in degree would seem to constitute a difference in kind. By and large, ergotamin helps only patients with migraine.

Study of the results in the various conditions represented in the non-migrainous group shows that, of the 7 patients relieved, 3 were in the group of 11 headaches of unknown cause (27% relief) and 3 were in the group of 8 postconvulsive headaches (37% relief). The large proportion of epileptic patients who were relieved brings

to mind the supposed underlying relationship of epilepsy and migraine, though more important may be the fact that postconvulsive headaches are naturally short lived. If our investigation had been carried on in a medical ward with "ordinary" spontaneous headaches, probably the percentage of cases relieved would have been higher than the observed 15% (though of the 10 subjects made worse by the injection, 5 belonged to this same unknown group, and 2 to the postseizure group). In none of the 5 cases given histamin did ergotamin lessen the severity or duration of the resulting headache.

Not only is ergotamin of little account in stopping non-migraine headaches, it may, according to Barger,[4] initiate a headache. To test this point we administered the drug to 38 subjects who were at the time free of pain in the head. Six (16%) of the subjects complained of resulting mild headache.

Aside from its effect on headache, the most prominent sequelæ of ergotamin administration are nausea and vomiting. The comparative incidence of gastric symptoms in the three groups of subjects was as follows:

	Number.	Percentage having:	
		Nausea.	Vomiting.
Without headache	38	47	18
Non-migrainous headache	46	56	37
Migraine	89	77	60

The epigastric discomfort of some of the subjects was too indefinite to be called nausea. Vomiting, when it occurred, was an objective symptom and in the headache groups bore some direct relationship to the proportion experiencing relief. However, in individual cases, there was no constant relationship between relief of headache and the presence of gastric symptoms.

Blood pressure and pulse rates were not recorded in all cases. As in migraine patients, the majority of patients with other types of headache or with none, had an increase in systolic blood pressure and a decrease in pulse rate, but changes in pressure and in pulse rate did not seem to be related to the therapeutic effect of the drug.

Comment. Quinin is called a specific against malaria, though it does not invariably stop malarial paroxysms and though it may favorably affect non-malarial fever. In the same sense, ergotamin tartrate may be spoken of as a specific for the relief of migraine headache. It evidently interrupts the morbid process which results in pain in the head, chilliness and malaise.

What is this morbid process? Beginning with Trautmann,[3] various authors have spoken rather glibly of an antagonistic effect of ergotamin on overactivity of the sympathetic nervous system. This might be conceived of as a release of spasm of cerebral vessels or as a direct action on sensory nerve endings. It is true that injection of ergotamin tartrate is followed by an increase in cerebro-

spinal fluid,[5] in systemic blood pressure and in cerebral blood flow,[6] but none of these changes seems sufficient in itself to explain the relief afforded.

It is possible that there is abnormal behavior of bloodvessels of the dura mater which does not show in records of total cerebral blood flow or of intracranial pressure, and that ergotamin might influence the dural vessels or the nerves which carry impulses from them. Evidence in favor of this view is the observation of Pool and Nason[7] that ergotamin in cats caused constriction of arterioles of the skin and dura, but not those of the pia. Pickering[8] believes that the severe throbbing headache which follows histamin injection arises in the bloodvessels in the dura, for removal of the Gasserian ganglion on one side anesthetizes the dura and prevents the appearance of histamin headache on that side. Less convincing is the clinical evidence of Dickerson,[9] who "cured" hemicrania by ligation of the middle meningeal artery on the side affected, and of Penfield,[10] who secured relief for 2 migraine patients by section of the ophthalmic fibers of the Gasserian root, the chief nerve supply to the dura (after superior sympathectomy had failed).

The evidence gained from our own experience has not supported the hypothesis of ergotamin as a paralyzer of the sympathetic nervous system. One patient had had interruption of accessible sympathetic pathways without relief of pain; yet ergotamin stopped her individual attacks. One of us[11] has observed that relief of migraine headache by ergotamin is not attended by alteration of sympathetic activity as judged by measurements of the electrical resistance of the skin.

If Pickering is correct in his belief that histamin headache arises in the vessels of the dura and if this is the point of origin of migraine headache, ergotamin tartrate should be effective in preventing or modifying histamin headache. It failed to do this in the cases tested by us, and by Pickering (personal communication). As a further test we injected histamin into 4 migraine patients whose attack had just been aborted by ergotamin. In every case a characteristic throbbing, short-lived histamin headache occurred.

Summary. Ergotamin tartrate is about 90% effective in aborting individual migraine headaches. The drug was injected into 46 patients having a non-migrainous headache; 15% were relieved; 63% were unrelieved, and 22% were made worse. Of 38 persons without headache who were given the drug, 16% developed a headache.

Nausea and vomiting occurred less frequently in persons having a non-migrainous headache or none, but in individual cases the effect of ergotamin on headache could not be related directly to the presence of gastric symptoms.

In 4 migraine patients relieved of headache by ergotamin, injection of histamin produced the usual histamin headache.

Ergotamin tartrate has a specific action in headaches of the migraine type. The evidence at hand indicates that the action is not directly on sensory nerve endings in the dura or skull, but that there is an intermediate systemic action.

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COMPARISON OF PROLAN BIOASSAYS IN TERATOMA AND OTHER CONDITIONS.*

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The purpose of this report is to present an analytical study of the conditions associated with an increased urinary output of the sex hormones (prolan A and prolan B), with special reference to teratoma testis. Emphasis is placed on the clinical value of these biologic hormone assays.

The results presented in this study are based upon over 500 completed tests necessitating about 15,000 accurately spaced and measured intraperitoneal injections into approximately 3000 mice.

* Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the writers.

The Aschheim-Zondek reaction is now widely used in the diagnosis of pregnancy. Recently, however, the principles of this assay have been applied as a diagnostic aid in teratoma testis. Single case reports showing excessive urinary prolan output associated with teratoma testis exist in the literature: Heidrich and Fels,[1] Kantrowitz,[2] Lilienthal,[3] Pachkis,[4] Hady,[5] Bollag,[6] Weinstein and Schofield,[7] and Johnson and Hall.[8] Reports of series of cases have been presented by Zondek,[9] Ferguson,[10] Stelle,[11] Owen,[12] Herger and Thibaudeau,[13] and by Cutler and Owen.[14]

Technical Consideration. Qualitative determination of the sex hormones in the urine, other body fluids, or extracts as applied in the diagnosis of pregnancy consist of injecting such fluids into suitable test animals and at a later date examining the sex organs for changes. Aschheim[15] employed immature female mice, Friedman[16] used non-pregnant rabbits, Brouha *et al.*[17] suggested male mice, while Curtis and Doisy[19] use adult öophorectomized or immature female rats. Recently Kanter *et al.*[18] reported a small fish, the bitterling (Rhodeus amarus) as a suitable test object.

TABLE 1.—THE RABBIT-MOUSE CORRELATION VALUES INDICATING THE LIMITATIONS OF THE RABBIT TEST FOR TERATOMA TESTIS.

Case.	Rabbit test.	Mouse test.
A	Negative	500
B	Negative	200
C	Questionable	2,000
D	Negative	2,000
E	Negative	1,000
F	Negative	500
G	Positive	2,500
H	Positive	16,000

Rabbit tests in this series all by single intravenous injections of 10 cc. of fresh urine. The mouse test results are stated in mouse units per liter of urine; 200 or above mouse units constitute a positive indication of teratoma testis.

To provide comparative results it is essential to have an assay capable of giving quantitative findings. The single rabbit test is but a qualitative assay. Since the majority of urines from patients with teratoma assay less than 2000 mouse units per liter, the usual rabbit test employing a single injection of 10 cc. or less of urine would be negative, as has been shown in this laboratory (Owen and Cutler[20]). Results obtained in this laboratory show the fish test to be inaccurate and similar findings are reported by Kleiner *et al.*[21] and by Szusz.[22] The immature female mouse is a serviceable test animal, as has been shown by Ferguson,[10] Owen,[12] and others. Approximate comparison dosage ratios for the various test animals have been determined. For the prolans and other water-soluble endocrins of like nature the dosages vary in proportion to the animal weight with the exception of fish.

A complete description of the assay procedure used in this study is given by Cutler and Owen.[14] Essentially such assay employs

6 immature female mice. By means of appropriate extracts a dosage range of 0.5 to 10 cc. of urine is obtained. Due to the double effect of follicle stimulation and luetinization, the readings of the test give the following quantitative determinations of the prolans in mouse units per liter of urine: 100, 200, 400, 500, 1000, 2000, 2500, 5000 and 10,000.

We have found that morning urines from teratoma patients are apt to contain more hormone per liter than do samples from the 24-hour outputs. Davy and Nason[23] have noted similar findings for the urine from pregnant women. Since the total amount of hormone actually excreted varies but slowly, it is necessary to obtain the volume of the 24-hour-output and to use a fractional part of this for assay purposes whenever possible. With this information calculation of the total daily output of hormone is facilitated and errors in the amount of hormone per liter of urine are avoided.

TABLE 2.—SHOWING THE DOSAGE RATIO IN MOUSE UNITS FOR THE VARIOUS LABORATARY TEST ANIMALS COMMONLY USED.

Subject employed.	Mouse units for positive.	Reference source.
Mouse	1	
Rat	10	Lewis and Geschikter.
Rat	3	Gardner *et al.*
Rabbit	22	Owen.
Fish, male	4 to 10	Calculated from Kanter *et al.*
Fish, female	8 to 16	Calculated from Kanter *et al.*

Spoilage or decomposition of the urine does not seem to affect the hormone materially, but such urines are apt to be toxic to the laboratory animals. A suitable preservative should be employed. The specimens mailed to the laboratory contain 1 drop of tricresol in 2 ounces of urine.

Conditions Associated With Increased Urinary Prolan Output. Conditions other than pregnancy and teratoma have been associated with an increased urinary prolan output. Chorionepithelioma in the female as well as in the male is usually accompanied by excessive amounts of urinary prolan (Fortner and Owen[24]). Hirsch-Hoffman[25] reported 3 cases of cerebral tumors and a case of acromegaly in females showing positive prolan findings. Kraus[26] cites Biedl and Morgetay-Becht as finding positive prolan assays in two-thirds of the acromegaly cases studied. He also reported 19 of 29 cases of elevated intracranial pressure as showing a positive urinary prolan test. Ziserman[27] lists hyperthyroidism and other conditions in the female as liable to give false positive pregnancy tests. Zondek[28] cites castration as showing occasional false positives. Castration either by surgery or by Roentgen rays may cause false positive reactions and, although prolan A (follicle stimulating hormone) may be present, the urines of castrates are said not to contain

prolan B (the luteinizing factor). Dodds[29] states that castration results in an increase in the amount of anterior pituitary hormone in the patient's blood. He also cites 4 instances of pituitary gland tumors as giving negative assay findings. Ehrhardt[30] lists rapidly proliferating tumors as myoma, carcinoma and genital hypoplasia as giving false positive pregnancy test. Maser and Hoffman[31] state that compensatory pituitary hyperfunction accompanying sexual deficiencies may give rise to false positive pregnancy tests.

In spite of so many possible interfering conditions, it is generally accepted that the usual Aschheim-Zondek reaction gives above 90% correct findings in the diagnosis of pregnancy (Aschheim,[15] Dodds,[29] Weisner[32] and others).

TABLE 3.—DISPLAYING THE PROLAN A FINDINGS IN NON-TERATOMATOUS PATIENTS. THE ASSAYS ARE GIVEN IN MOUSE UNITS PER LITER OF URINE.

Cases.	Diagnosis.	Quantitative assays.				
		Negative.	100.	200.	400.	500.
6	Cyst, testis	11	1	2	1	
2	Luetic	4				
1	Myxosarcoma	2				
1	Granuloma	2	2	..	..	1
1	Lymphosarcoma	1				
1	Ca. prostate	1				
1	Pseudomyxoma	5	..	1		
2	Pituitary dysfunction	2				
1	Gynecomastia	2				
5	Epididymitis	7	1	3		
1	Lymphoma	1				
4	Mixed tumor, parotid gland	8				
1	Squamous cell, keratinizing	2				
1	Paraffinoma	2				
1	Sacrococcygeal teratoma	3				
29		53	4	6	1	1

All positive tests were obtained on 4 cases: 1 cyst, 1 granuloma, 1 pseudomyxoma, 1 epididymitis. Serial checks on 3 of these cases gave consistent positive assays.

Many of the conditions which may interfere with the interpretation of the reaction occur in females; consequently, the possibility of false positive is minimized in males. The control series at this laboratory and others include over 500 negative assays on urines from normal males and from patients suffering with benign lesions of the testis (Cutler and Owen[14]).

The assay as planned approaches closely the findings associated with normal urines and it may be expected that incorrect positives will only be avoided by conservatism in interpretation of the results. Occasional false positives in the higher range mouse dosages were expected. It became necessary to qualify the interpretation, *viz.*, unless the 2 mice receiving the highest dosages are positive the test is questioned and repeated at a later date. One quantitatively low positive assay of itself is not wholly indicative of teratoma, but if a series of tests are positive and the quantitative results show

an increase in hormone, then the diagnostic value of the test is rarely to be questioned.

Results. In 71 cases later proven histologically to be teratoma, the findings in 340 tests ranged from negative (less than 100 mouse units per liter of urine) to 125,000 mouse units per liter of urine in a case of chorionepithelioma testis. Omitting 2 cases of chorionepithelioma testis the average finding was approximately 950 mouse units per liter of urine. Of the 71 cases of known teratoma, 69 showed one or more of the following conditions: a drop in the urinary prolan excretion following irradiation or surgery, an increased output on series tests, or tests consistently above 200 mouse units per liter of urine. Two patients with no pre-operative prolan test showed a negative postoperative prolan assay. Of the 69 cases, 37 showed an increased prolan finding on series tests, 51 displayed a drop in urinary prolan following irradiation or surgery; 26 showed tests consistently above 200 mouse units per liter of urine. In 17 instances following irradiation and/or surgery the test dropped to negative, while in 39 cases the post-treatment prolan dropped to 200 or less mouse units of prolan per liter of urine. In 7 instances irradiation therapy failed to cause a drop in prolan excretion. In 6 cases coming to autopsy the findings have verified the prediction of widespread metastases as indicated by the excessive prolan output, previous to death.

On 29 patients with pathologic conditions other than teratoma located in the testes 64 tests revealed 3 instances of false positives. These false positives occurred in 1 instance each of cyst, epididymitis and granuloma. All 3 cases had previous orchidectomies, thus the findings may be due to the partial castration. The percentage of false positives is less than 10.

Of 25 other cases now in process of diagnosis, clarification reveals 16 are definitely negative and 9 have positive assays ranging from 200 to 50,000 mouse units of prolan per liter of urine.

A majority of our cases have had orchidectomies at other hospitals previous to their admission here for treatment; yet the prolan assay usually decreases following the irradiation therapy, demonstrating that the test might be used as a means of detecting metastases as well as the original teratomas.

Comment. The assay of urinary prolans in cases of teratoma testis adds a practical diagnostic aid to the armamentarium of the laboratory. Since irradiation of such tumors is followed by a decrease in the urinary prolans in the majority of cases, the effectiveness of treatment may also be judged. The test thus serves as a guide in the diagnosis, prognosis and treatment of teratoma testis.

False negatives or false positives have occurred in less than 10% of the assays in this series, indicating that the assay as planned and conducted is as suitable a diagnostic aid for teratoma as the original less quantitative Aschheim-Zondek reaction is for the diag-

nosis of pregnancy. By careful interpretation and serial tests it is possible to increase the accuracy of the assay as a diagnostic aid.

The routine use of the bioassay at this hospital has demonstrated its practical value. Over 125 suspected teratoma testis cases have benefited by the findings of the test. The laboratory now serves as a testing center for the various Veterans' Administration Facilities as well as for the patients hospitalized here. A mailing service for specimens has been instituted to aid in the follow-up of discharged patients.

Summary. 1. Quantitative determinations of the urinary prolans in 125 cases of suspected teratoma testis have been made.

2. In general, patients suffering with teratoma testis excrete more than 100 mouse units of the prolans per liter of urine.

3. False negatives or false positives occur in less than 10% of the cases; thus the test is as accurate as the usual laboratory test.

4. A review of other conditions reported to be associated with excessive urinary prolan output is presented.

5. Original teratomas, local recurrence or metastases are associated with increasing prolan findings as displayed by serial assays.

6. A marked diminution in the prolan output usually follows irradiation or surgery.

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SPONTANEOUS PNEUMOTHORAX SIMULATING ACUTE ABDOMINAL AFFECTIONS.

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Simulation of acute abdominal disease of a surgical nature by thoracic affections with referred pain is a matter of more or less common knowledge. The close resemblance at times between lobar pneumonia, acute fibrinous pleuritis, coronary thrombosis, acute fibrinous pericarditis and the "acute surgical abdomen" is emphasized in practically every text. The same can be said regarding lesions of the spine and spinal nerves as osteomyelitis of the thoracic vertebræ, intercostal neuralgia, etc. Other affections of the chest, such as acute cardiac decompensation (producing presumably sudden hepatic engorgement), ruptured or dissecting thoracic aneurysm, pulmonary infarct, acute mediastinitis and spontaneous rupture of the esophagus although infrequently mentioned are also almost universally recognized as mimics of primary abdominal disease.

Spontaneous pneumothorax masquerading as an abdominal affection is apparently regarded as extremely rare by or is not known to most writers, since it is generally omitted in treatises dealing with abdominal and thoracic diagnosis. No reference to pneumothorax simulating the "acute abdomen" can be found in any of the many excellent American texts or systems of surgery. The same is true of continental handbooks. In only one English publication, by Adams,[1] is pneumothorax mentioned among the intrathoracic affections which are capable of producing the picture of an acute abdominal illness. Adams does not, however, cite any specific example. A careful survey of the medical periodical literature leads to the disclosure of only 4 reports, each of which contains the description of one instance of spontaneous pneumothorax where the erroneous diagnosis of primary abdominal disease was made.

There is reason to believe that the incidence of pneumothorax simulating the "acute surgical abdomen" is not as low as the literature seems to indicate. The writers have personally observed in a relatively short period of time, 3 characteristic examples (2 in a large, general hospital and a third in private practice)—the explanation for this rather unique experience lying probably in the frequency with which they resort to the Roentgen ray. In all questionable or atypical abdominal cases, the fluoroscope supplemented at times by plates is employed as part of the routine examination. It is not unlikely that without the aid of the Roentgen-ray the correct diagnosis of pneumothorax might not have been established in some of our cases and the presence of non-existent abdominal disease assumed. Since so few actual instances of pneumothorax simulating acute abdominal affections are recorded, it is deemed advisable to summarize those published by others and to describe briefly the ones observed by ourselves.

Summary of Cases Reported by Others. 1. *Siebner's*[2] *Case.* A man, aged 32, experienced extremely severe sudden epigastric pain, occurring while riding to work. The pain which radiated to the left shoulder was associated with nausea. Upon admission the patient appeared to be in "shock." The temperature was 99.5° F. and the pulse 100 per minute. Respirations were shallow and only slightly accelerated. The heart and lungs were normal except for slight decrease of the breath sounds at the left base. The abdomen was boardlike, retracted and very tender. The liver dullness was not obtained with certainty. The diagnosis of perforated peptic ulcer was made and an immediate operation performed. No lesion of the stomach or other abdominal structure was discerned. The following day, the first signs of a left pneumothorax were elicited. Eight days later a Roentgen ray revealed a complete left pneumothorax. The patient passed through an uneventful convalescence, and at the end of the third week, only a small amount of air and fluid remained in the left pleural cavity. The sputum was persistently negative for tubercle bacilli. The patient has been well since.

2. *Beardsley's*[3] *Case.* A young man of 26, while in a tuberculosis ward, was suddenly seized by severe, knifelike abdominal pain. Two hours after the onset the author found the patient sitting in bed with his head bent forward between his knees, groaning with pain and covered with cold perspiration. At first the pain was localized and was situated to the left of the umbilicus but later spread to involve the entire left abdomen. The temperature was subnormal, the pulse 140 per minute, and the respirations only slightly accelerated. One hour after administration of ½ grain of morphin, the patient was comparatively free from pain unless movement occurred. The abdomen was distended, rigid and tender. A diagnosis of perforated tuberculous ulcer was made but the patient's condition did not permit surgical intervention. Except for an increase of the abdominal distention, the patient continued with the same symptoms and signs for 2 days following which he died. At no time was dyspnea present. At autopsy, although there were many tuberculous ulcers present in the intestine, none had perforated and no peritonitis was found. There was, however, a left sided pneumothorax which was the only lesion to account for the abdominal symptoms.

3. *Oechsli and Skillen's*[4] *Case.* A woman aged 25, developed during the fourth month of her stay in a tuberculosis hospital, intense epigastric pain,

a severe chill, fever of 103° F., a pulse rate of 125 and a respiratory rate of 28 per minute. The pain was so violent that even morphin gave but little relief, and at onset was associated with nausea and vomiting. The following day the emesis recurred and the pain persisted. No noticeable dyspnea or cough was present. For the next 5 days there was only a slight change in the patient's condition. The pain in the epigastrium continued and was accompanied by occasional slight pains in the left chest. Two days later, extreme hyperresonance was found over the lower left chest and a Roentgen ray showed a collapsed left lung. The patient recovered from the pneumothorax.

4. *Hurxthal's*[5] *Case.* A man of 29 had suffered for 2 to 3 years from epigastric discomfort occurring 2 hours or so after meals. The pain was relieved by the ingestion of food and also soda. On June 30, 1928, while attempting to unloosen a seat of his automobile, he experienced a sharp pain in his right shoulder. He took to bed and obtained some relief. After a few hours of bed-rest the patient attempted to drive his car, whereupon an increase of the shoulder pain occurred and dyspnea and abdominal pain appeared. Upon entrance to the hospital, the patient appeared quite ill. The breathing, however, was not labored but there was appreciable cyanosis. The pulse was thready, the rate 120 per minute and the blood pressure was 80 systolic and 70 diastolic. The abdomen was rigid and painful to pressure, especially in the epigastrium and in the right upper quadrant. These observations together with the presence of abdominal pain and a typical chronic ulcer history suggested the diagnosis of perforated peptic ulcer. However, when the chest was carefully examined it was found that the right side was larger and exhibited less respiratory mobility than the left and that over the right chest there was hyperresonance except at the base posteriorly where there was shifting flatness with absence of fremitus and breath sounds. The acute illness was then attributed to a right pneumothorax, the chronic ulcer syndrome apparently being unrelated.

Authors' Case Reports. Case 1. M. S., a white male of 50, while about to drive a golf ball on June 9, 1929, was suddenly seized with right upper abdominal pain which lasted a few minutes and then ceased spontaneously. He then walked about 200 yards when he experienced a recurrence of the abdominal pain which persisted and became associated with distressful and labored respirations. After a brief period, he was able with assistance to walk back to the club-house and there while dressing he became dizzy and vomited a huge quantity of gastric contents. Following morphin, the patient was transported home. The abdominal pain and dyspnea continued and in addition he vomited 3 times. A physician who saw the patient at his house diagnosed a perforated ulcer. When seen by one of us (H. A. S.) a few hours after onset of his illness, the patient was suffering from severe upper abdominal pain and respiratory embarrassment. The abdomen was slightly distended and moderately rigid and tender especially over the right upper quadrant. The pulse and respirations were accelerated but the temperature was normal. A perforated ulcer seemed plausible.

Close observation of the markedly emphysematous chest elicited that on the right side the respiratory excursion was somewhat limited and that the breath sounds were diminished as compared to the left. There were a few moist and many dry râles throughout both lung fields. A history of a long-standing bronchitis and bronchiectasis was obtained. There had been no previous digestive complaints to suggest ulcer. A diagnosis of right pneumothorax due to a ruptured emphysematous bleb was made and conservative treatment advised. The marked tenderness over the right upper quadrant was ascribed to engorgement of the liver which organ was indistinctly felt below the costal border. The following day the patient's temperature

rose to 102° F. and the physical evidences of a pneumothorax became manifest. A Roentgen ray showed abnormal clarity of the affected side and retraction of the lung characteristic of pneumothorax. No fluid was present in the chest cavity. After 12 days the patient recovered from the pneumothorax.

Case 2. C. Z., a man of 37 entered the Cook County Hospital on December 17, 1932 with the following history. On December 11, he contracted a "chest cold," manifested by thoracic pain, cough and expectoration, on which account he remained in bed. During the early morning hours of December 16, the patient was suddenly seized with a very severe, sharp pain in the upper abdomen which caused him to roll about, cry out and moan. The pain seemed to compress his abdominal contents and to shut off his breath. After several minutes, the pain ceased spontaneously but returned in about 20 minutes. Vomiting occurred once at the onset. The abdominal pain recurred at intervals throughout the night. The patient stated that he felt the least pain while he sat upright with his thighs flexed on the abdomen. During the day of December 16, there were persistent soreness in the upper abdomen and vomiting. There was nothing in the past history prior to the onset of the "chest cold" to suggest tuberculosis.

At the time of admission he appeared acutely ill and coughed frequently. The pulse rate was 82, the temperature 98° F. and the respirations 24 per minute. The two sides of the chest moved equally on deep breathing. Over the inferior portion of the right chest the resonance was impaired and the breath and voice sounds greatly diminished. The heart was essentially normal. The abdomen was full in the upper half where both rigidity and tenderness were present. Peristaltic sounds were diminished. The liver edge was felt two fingers below the costal margin. The blood picture was normal except for indications of a secondary anemia. The two physicians who examined the patient shortly after admission were unable to decide whether the abdominal pain was due to a perforated peptic ulcer or to a basal pleuritis. When called upon to attempt the differentiation, the authors fluoroscoped the patient and observed a partial pneumothorax on the right side. A roentgenogram taken the following day (Fig. 1) revealed a greater accumulation of air on the right side and evidence of an old fibro-calcareous tuberculosis on the left. The patient recovered slowly from the acute episode.

Case 3. D. W., a man of 37, entered the Cook County Hospital on June 28, 1930, with the history that 6 hours previously he was awakened by nausea followed by vomiting. Immediately after the emesis he felt a severe, lancinating pain in the epigastrium which radiated around and upward to the interscapular region of the back. The pain continued severe and even two hypodermic injections of morphin failed to afford relief. The patient preferred the sitting to the recumbent position. Vomiting recurred 3 times. Inquiry into the past history elicited the information that the patient had experienced occasional post-prandial epigastric burning relieved by food and soda. No information was obtained which was suggestive of past or present tuberculosis.

The physical examination disclosed an acutely ill white male with a temperature of 99° F., a blood pressure of 170 systolic and 120 diastolic, and pulse and respiratory rates of 120 and 48 respectively. The tactile fremitus, breath sounds and resonance were found diminished on the left side from the angle of the scapula downward. The abdomen was flat, markedly tender and rigid in the upper quadrants. The liver dullness was apparently unchanged. Peristaltic sounds were greatly diminished. The white cell count was 18,000.

Opinions as to the diagnosis varied. While the advisability of laparotomy

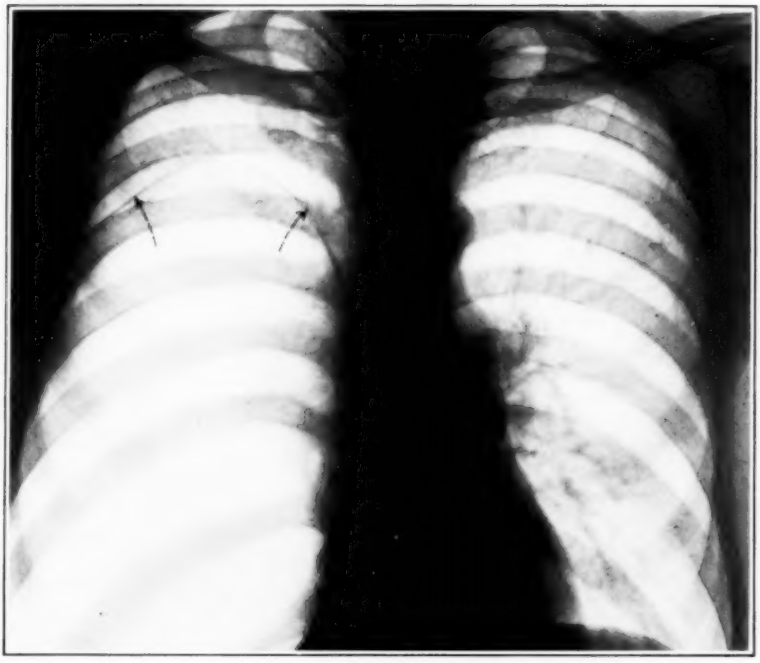

FIG. 1.—Valvular pneumothorax which clinically simulated an acute abdominal affection (authors' case reports, No. 2). The depression of the diaphragm by displacing the liver downward resulted in the presence of tenderness and resistance in the right hypochondrium. Adhesions prevent complete collapse of the right lung and displacement of the mediastinum to the left. The lower border of the right lung is indicated by arrows. Fibro-calcareous, tuberculous markings are observed in the left lung field.

was being discussed, the patient was fluoroscoped and a rather well developed left hydropneumothorax demonstrated. Nothing further could be determined since the patient died 4 hours after entrance and permission for necropsy was refused.

Comment. A study of the foregoing case histories leads to the realization of the difficulty one may encounter in distinguishing a sudden pneumothorax from an acute surgical abdomen. In the first place the clinical picture of rupture of the lung may be chiefly an abdominal one. Intense abdominal pain, nausea and vomiting, associated with tenderness and rigidity which were present in the cases recorded, constitute a syndrome which generally demands immediate laparotomy. Particularly is attention likely to be focussed on the abdomen when a history of previous gastro-intestinal disturbance is obtained, as in 4 of the 8 cases reviewed. In the second place, thoracic symptoms such as occur characteristically in pneumothorax are frequently observed in acute surgical affections of the abdomen. For instance, the occurrence of sudden pain following violent exertion, the reference or radiation of pain to the shoulder region, dyspnea, collapse, and the assumption of the sitting position with the legs drawn upward all are commonly met with in perforated peptic ulcer.

The error of regarding a sudden pneumothorax as an abdominal lesion can almost invariably be avoided. A careful chest examination of each patient with an atypical picture of abdominal disease will eliminate a large percentage of mistaken diagnoses. Unfortunately, only too frequently when the symptoms point to an affection within the abdomen the chest is examined in a perfunctory manner or even neglected altogether. A certain amount of skill in physical diagnosis is often a prerequisite for the correct interpretation of the underlying disease. It is true that an advanced pneumothorax with almost complete collapse of the lung does not require a virtuoso but when the pneumothorax is partial it may elude the most expert. Close attention to the abdominal signs may reveal the tenderness to be merely hyperesthesia and the muscular rigidity to be only apparent and not continuous. However, here again some experience and skill on the part of examiner is indispensable. Of particular value in directing the attention of the physician to the possibility of a pneumothorax is the history of previous pulmonary disease especially tuberculosis.

For the detection of an unrecognized pneumothorax, the Roentgen ray is of extreme importance. When the symptomatology is atypical and the physical signs are difficult to elicit, it is likely that only a small percentage of the instances of pneumothorax are discovered by clinical means. The use of the fluoroscope may suffice to demonstrate the pulmonary collapse but not infrequently proves inadequate. A limited collection of free air may be difficult to identify unless fluid is simultaneously present in the chest cavity.

The resulting fluid level is then readily observed in the fluoroscope and can be made to shift with change in position of the patient. However, the escape of fluid may not occur until late in the course of illness or not at all. It is therefore, necessary in questionable cases to take plates. The exposure is best made at the height of forced expiration in which state the pneumothorax is rendered most apparent. Since sudden pneumothorax tends to simulate most closely ruptured peptic ulcer, the Roentgen ray examination serves a double purpose. The Roentgen ray is capable of demonstrating the presence or absence not only of a pneumothorax but also that of a pneumoperitoneum. Fluoroscopic examination is quite sufficient to detect free intraperitoneal air and requires only a few moments. The value of the Roentgen ray in the diagnosis of perforated peptic ulcer, including details of the technique, interpretation, etc., has been discussed elsewhere (Vaughan and Singer[7]).*

Summary. Sudden pneumothorax simulating an acute surgical affection of the abdomen is not a particularly rare occurrence. Three instances have been encountered by the authors. The danger of mistaking spontaneous pneumothorax for a surgical emergency can usually be avoided if the possibility of sudden rupture of the lung is included in the diagnostic considerations. The mere thought of pneumothorax will not always suffice as slight or partial pneumothorax is likely to elude the average examiner. The most effective means of avoiding error is by resort to the Roentgen ray. Fluoroscopy alone may be adequate, especially if a hydropneumothorax is present when a shifting fluid level may be visualized. In many instances however, plates are indispensable for demonstration of the escaped air. The pneumothorax is rendered most apparent when the exposure of the film is made at the height of expiration.

* Since the time this article was submitted for publication, the following report has appeared in print: Joress, M. H.: Spontaneous Pneumothorax (Rupture of the Lung) with Abdominal Symptoms in the Course of Artificial Pneumothorax—A Report of Two Cases, Am. Rev. Tuberc., **33**, 98, 1936. The diagnosis in both instances was rendered less difficult than usual due to the knowledge of a pre-existent pulmonary tuberculosis.

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A METHOD FOR DETERMINING THE SEDIMENTATION RATE AND RED CELL VOLUME IN INFANTS AND CHILDREN WITH THE USE OF CAPILLARY BLOOD.

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The majority of methods designed for the determination of the sedimentation rate of the red blood cells depends upon the use of venous blood. While the large quantities of blood obtained in this way simplify the manipulation of the test, practical difficulties are encountered when venipuncture is attempted in infants and young children. This is particularly evident when repetition of the test at short intervals is required. In rheumatic disease, for example, in which the determination of the sedimentation rate is utilized as a guide to the progress of the condition, the distress of the young patient which accompanies venipuncture often restricts the number of tests that should be carried out for comparative purposes.

A large number of micromethods, in which capillary blood is employed, has, therefore, been devised in order to overcome these obvious disadvantages, with results approximating those of macromethods. There are several considerations, however, which have interfered with their more widespread use. The employment of minute quantities of blood often requires considerable dexterity and practice. The tendency to clot formation, due to delayed or insufficient admixture with the anticoagulant, results in irregularity of the sedimenting column. An additional factor responsible for discrepancy in results with the two types of tests is the influence of capillarity exerted within the lumen of the narrow tube or pipette, in which the rate of sedimentation is measured, which constitutes an integral part of a micromethod. Another inadequacy is that there is usually no provision for estimating the corpuscular volume percentage, an important factor with rapid rates of sedimentation.

The introduction of another sedimentation tube, in spite of the multiplicity of methods that already exists, therefore seems justified. The purpose of this paper is to present a practical, simplified and reasonably accurate method for estimating the sedimentation rate with the use of capillary blood, which, however, embodies the basic specifications and features of a standard venipuncture method. In a series of observations with the blood of infants and children, the test with few exceptions has proven of definite value as an additional guide in supervising the illness and convalescence of the sick

child. Unexplained results have at times been obtained, but the same situation occurs with any laboratory procedure.

No attempt will be made to review in detail the vast literature concerning the theoretic basis for changes in the suspension stability of blood. It is generally agreed that a rapid rate of sedimentation during the course of infection depends upon an increase of the plasma fibrinogen and globulin with which disease processes are associated. The effect of variations in electric charges on agglutination of erythrocytes is doubtless a fundamental contributing factor.[1] But of more practical importance is the provision that the size and number of the red cells fall within certain limits, since a rapid sedimentation rate occurs in anemic states independent of infection.

Technique. The tube that has been specially designed represents a modification of the features of the Cutler micro-[2] and macromethods[3] and of the Wintrobe tube[4] used with small quantities of blood. It constitutes in effect a macrosedimentation tube of reduced dimensions rather than a microsedimentation tube of the type in current use since the latter implies apparatus possessing a capillary bore and requiring a single drop of blood. The tube described in this paper (Fig. 1*c*)* will, however, be referred to as one for microsedimentation since it utilizes capillary blood as contrasted with macrotubes in which venous blood is examined. Its diameter is approximately 2.5 mm., which corresponds to the minimum requirement for the micromethod.[5,6] It is graduated like the Cutler tube into 50-mm. divisions with a capacity within the measured area of less than 0.25 cc. of blood. Above this zone, the tube is widened into a small cup, the rim of which serves to guide the stem of the pipette with which the blood is transferred from the collecting tube This feature also facilitates cleansing.

A variety of anticoagulant have been used in sedimentation tests. Although heparin, which is regarded as the ideal substance,[7] was utilized for comparative tests in this study, a solution of 5% sodium citrate was ultimately adopted because of its availability and its nominal cost. Other concentrations of sodium citrate, as well as mixtures of oxalates, have been suggested by various writers. It was observed, however, that the results with the use of a minimal and measured quantity of 5% sodium citrate compared favorably with those of macromethods. Westergren[8] pointed out that the sedimentation rate with 3.8% sodium citrate used in his test differed to a slight degree only from that with the 5% solution.

The sedimentation test with the use of finger blood, described by Cutler,[2] involved the use of a pipette whose bore and stem dimensions were similar to those of the tube employed in this study. A primary difficulty with the Cutler micromethod, however, rose from its dependence upon traces of sodium citrate solution adhering to the walls of a small storage tube to prevent the blood from clotting. In addition, considerable technical skill and dexterity were required in order to retain the measured specimen within the stem of the pipette until a spring attachment could be applied in order to seal off the bottom.

A special pipette (Fig. 1*a*) was, therefore, designed for drawing up capillary blood similar to the one employed for hemoglobin determinations by the Sahli method. Two graduations are present, one at 0.04 cc., the other at 0.1 cc., the latter representing the total calibrated capacity of

* The complete apparatus required for the test may be obtained from E. Machlett & Son, 220 East 23rd Street, New York City.

the pipette. The pipette is sufficiently long so that capillarity is maintained within it. This feature is of particular importance so that blood already withdrawn is not lost in the event of sudden movement of the child.

The first step in the procedure is to moisten the inside of the entire pipette by drawing 5% sodium citrate throughout its length several times and eventually discarding all but 0.04 cc., which is the first graduation on

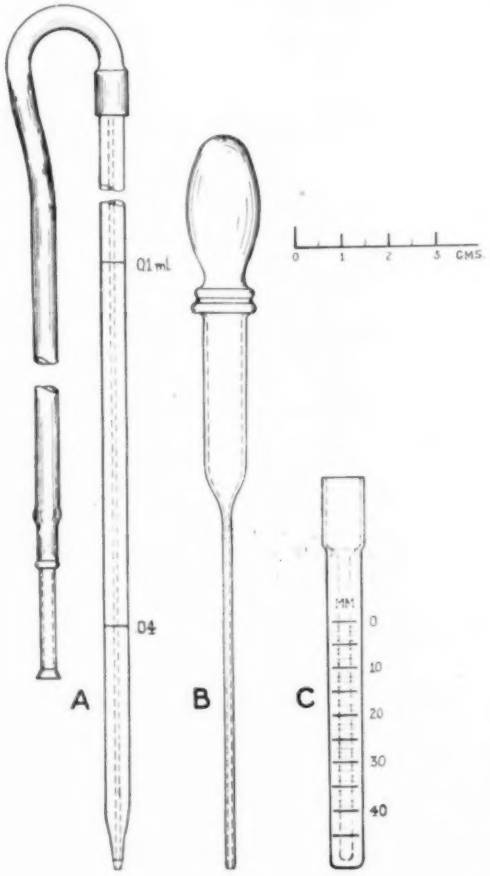

FIG. 1.—*A*, Pipette for measuring the citrate solution and for collecting blood; *B*, pipette with bulb for transferring citrated blood to, *C*, sedimentation tube.

the pipette. The latter quantity is expelled into the bottom of an ordinary test tube and is sufficient to prevent the coagulation of 0.3 cc. of blood. Blood for the test is obtained by puncture of the finger tip of the child, or of the heel in the instance of the young infant. The puncture site is carefully prepared and a sharp needle is used, or preferably, an automatic lancet, since the latter secures a free flow of blood which is an essential prerequisite for accuracy of the test. Moderate pressure of the finger tip or heel in order to secure a complete specimen did not interfere with the test.

Blood is withdrawn (0.3 cc.) by 3 consecutive aspirations of 0.1 cc. with the pipette, using rubber tubing for suction as for a blood count. As each 0.1 cc. of blood is collected, it is transferred to the test tube and shaken vigorously to secure thorough admixture with the sodium citrate solution. Following the expulsion of the second 0.1 cc. some of the citrated blood is sucked up the pipette throughout its length and then returned to the test tube. After the addition of the final 0.1-cc. fraction of blood, the tube is corked, and the contents are thoroughly admixed once more. The test may be performed at once or may be postponed for several hours. Should the specimen clot within the test tube, it is due to inadequate finger puncture, the preliminary introduction of less than 0.04 cc. of citrate solution, or to failure to agitate the blood thoroughly so as to secure complete interaction with the anticoagulant.

The citrated blood is transferred to the sedimentation tube by means of a simple capillary or Wright pipette with an attached rubber bulb (Fig. 1*b*). This type of pipette is readily prepared in the office or laboratory from ordinary soft glass tubing, and is of sufficient width to receive the small rubber bulb in common use. The capillary portion must be adequate to reach the bottom of the sedimentation tube. The latter is filled by the gradual release of the citrated blood by gentle pressure on the bulb as the pipette is slowly withdrawn from the bottom of the tube until the uppermost "0" mark is reached. Any excess above this graduation is easily removed with the same pipette. The tube is placed in a rack and the rate of sedimentation is recorded. All tests were carried out at room temperature.

The time at which the readings are made vary with many observers. The "corrected sedimentation index" of Rourke and Ernstene,[9] which incorporates the most desirable refinements of the technique, requires the measurement of the rate during the phase of most constant sedimentation, distinct from the preliminary period of erythrocytic aggregation and the final one of packing. This method necessitates readings at periodic intervals, the plotting of a curve and subsequent correction for anemia. With the Cutler graphic technique[3] the level of the sedimenting column is recorded at 5-minute intervals for 1 hour. From these determinations, 4 types of graphs are constructed, each corresponding to a different degree of cellular destruction accompanying infection.

In order to simplify the test and to render it suitable for routine clinical use, the plan adopted in this study was to record the level of the upper layer of the sedimenting erythrocytes at the end of ½ hour and 1 hour. The two readings furnish an approximate idea of the velocity with which the red cells settle, although practically and for comparative purposes the single observation after 1 hour was sufficient.

Cleaning the tube was readily accomplished with the capillary pipette previously employed for transferring the citrated blood from the storage test tube to the sedimentation tube. Water was forced through to the bottom of the sedimentation tube several times by firm pressure on the bulb of the pipette until the return flow was clear. Alcohol and ether in turn were introduced and the tube was removed by forcible shaking.

In order to determine the efficiency of the microsedimentation tube described in this paper, comparison was made with a standard method using venous blood. The Cutler technique was chosen because of the similarity in the height and subdivisions of the graduated portion of both tubes.

Comparative tests (102) were carried out with the blood of 84 infants and children ranging in age from 12 days to 14 years, of whom 43 were sick and 41 healthy. For the macromethod 0.1 cc. of 3% sodium citrate solution and 0.9 cc. of blood obtained by veni-

puncture were mixed and expelled from the syringe into a Cutler tube of 1-cc. capacity graduated into 50-mm. divisions. In 95 instances, comparative tests with Cutler and microsedimentation

TABLE 1.—COMPARISON OF SEDIMENTATION RATES WITH CAPILLARY AND VENOUS BLOOD IN NORMAL INFANTS AND CHILDREN.

Case No.	Patient	Age		Date	Sedimentation rate.				Cell volume percentage anticoagulant.	
					Venous blood, Cutler method.		Capillary blood, author's blood.			
		Yr.	Mo.		30 min., mm.	1 hr., mm.	30 min., mm.	1 hr., mm.	Heparin, %	5% sodium citrate, %
1	K. A.	8	..	4/ 9/35	2	7	2	8	45	37
2	J. B.	3	6	11/ 1/34	6	11.5	6	12	42	34
3	B. B.	7	..	2/19/35	2.5	6	3	7	42	36
4	H. B.	..	5	2/22/35	2.5	7	2.5	6	45.5	42
5	R. B.	4	..	5/21/35	6	12	6	12	43	36
6	G. C.	7	..	10/ 9/34	6	10.0	7.5	12	45	40
7	N. C.	12	..	3/21/35	2	6	3	6	42.5	36
8	W. E.	..	11	2/11/35	4	10	4	10	41.5	32
				2/16/35	5	9	5	10	42	35
9	M. F.	5	..	12/ 2/34	5	8	5.5	9	44	35
10	T. F.	4	..	10/25/34	4	8	6	11	43	39
11	J. F.	..	13	3/ 7/35	7	12	6	12	44	35
12	F. F.	8	..	2/14/35	5	10	6	11	44	38
13	E. F.	10	6	10/30/34	3	8	6	10.5	45.5	40
14	M. G.	2	10	3/ 9/35	3	7	3	8	42.5	36
15	H. G.	6	..	11/20/34	5	11	7	12	40	33
16	I. H.	11	6	1/27/35	3	9.5	4	10	43	39
				2/ 5/35	4	7	4	8	43	36
17	E. H.	6*	..	12/14/34	5	11	5	11	37.5	34
18	M. H.	..	15	12/20/34	4	9	2	10	37.5	31
19	R. H.	2	..	11/ 5/34	1.5	6.5	1.5	6.5	43	36
20	K. K.	10	6	4/30/35	2	6	2	6	44.5	39
21	A. L.	9	..	10/11/34	2	8	2	9	44	36
22	W. Macf.	5	8	2/ 7/35	2	5	1.5	4	42	36
23	D. M.	7	..	6/20/35	6	12	7	13	41	32
24	A. M.	12	..	3/20/35	1	3	1	3	46.5	38
25	A. N.	9	..	2/23/35	2	6	2	6	43.5	36
26	J. McQ.	11	6	10/13/34	2	6	2.5	6	42	35
27	R. M.	2	..	1/ 7/35	7	12	7	12	38	32
28	G. M.	14	..	6/ 8/35	3	10	4	12	41	34
29	F. M.	..	17	5/14/35	5	10	5	11	40	31
30	R. P.	..	22	3/12/35	5	9.5	5	10	42	34
31	B. P.	12†	..	1/16/35	4	10	2.5	6	58	50
32	T. R.	6*	..	2/21/35	4	7	4	7	51	44
33	F. R.	11	6	1/29/35	4	9	6.5	10	47	38
34	G. R.	9	..	11/13/34	1	4	1	3	47	38
35	M. R.	12	..	5/23/35	4	7	5	8	42	37
36	G. R.	11	..	4/ 6/35	4	8	3	7	44	37
37	J. R.	10	..	6/22/35	8	13	8	13	41	35
38	H. S.	8	..	12/ 1/34	4	9	4	9	44.5	36.5
39	F. S.	9	..	2/19/35	7	11	7	11	47	38
40	R. T.	8	..	11/27/34	2	8.5	5	10	42	34
				12/ 4/34	4.5	9	4	10	44	36
41	J. V.	..	3	1/28/35	2	7	4	9	43	34
42	R. Z.	..	7	10/10/34	4	10.5	5	11	36	30

* Weeks. † Days.

tubes were carried out in which heparin* was substituted for sodium citrate solutions. In addition, 128 microsedimentation tests were carried out without comparison with the macromethod, except that

* A solution of heparin was prepared by dissolving 50 mg. in 2 cc. of distilled water. One drop dried in a test tube was sufficient for inhibiting coagulation of at least 0.3 cc. of capillary blood for the microsedimentation test, and 3 drops for 1 cc. of venous blood for the Cutler tube.

a duplicate microsedimentation test was performed with heparin as an anticoagulant.

The purpose of the tests with heparin was to compare the sedimentation rates as well as cell volume percentages after centrifuging, with values for citrated blood. Since heparin as anticoagulant does not hasten or retard the sedimentation rate as occurs with the sodium citrate and the other salt anticoagulants,[7] the results were of value from a comparative standpoint. At the termination of each sedi-

TABLE 2.—SUMMARY OF RESULTS COMPARING SEDIMENTATION RATES BY CAPILLARY AND VENOUS BLOOD METHODS.

Method.	No. cases.	No. tests.	Sources of blood.	Anticoagulant.	Sedimentation rate			
					30 min., mm.		1 hr., mm.	
					Average.	Extremes.	Average.	Extremes.
1. *Normal Group.*								
Microsedimentation	42	45	Finger*	5% sodium citrate	4.3	1–8	9.1	3–13
Cutler	42	45	Vein	3% sodium citrate	3.9	1–8	8.6	4–13
Microsedimentation	38	40	Finger	Heparin	5.5	1–13	12.0	3–21
Cutler	38	40	Vein	Heparin	4.7	0–13	10.1	3–21
Summary of microsedimentation tests†	60	72	....	.....	4.2	1–8	9.1	3–13
2. *Pathologic Group.*								
Microsedimentation	43	57	Finger	5% sodium citrate	15.1	3–33	20.8	8–35
Cutler	43	57	Vein	3% sodium citrate	14.6	3–34	20.6	8–35
Microsedimentation	43	55	Finger	Heparin	15.2	3–32	22.2	11–33
Cutler	43	55	Vein	Heparin	15.8	1.5–32	22.2	9–33

* Blood was obtained from the heel in very young infants.

† These tests were performed according to the technique described in the text with the use of capillary blood after treatment with 5% sodium citrate.

mentation test the tubes with heparinized and citrated blood were centrifuged at a speed of 2500 revolutions per minute for 30 minutes. The number of millimeters of packed cells multiplied by 2 constituted the cell volume percentage. The latter values with heparin were on the average 7.5% higher than with sodium citrate (Table 3), due to the fact that the former expresses the results with whole blood whereas the latter is derived from that of a diluted specimen (0.4 to 0.3 cc. of blood). Furthermore, the erythrocytes undergo shrinkage with sodium citrate and other inorganic salts as contrasted with heparin which does not affect them.

A total of 240 microsedimentation tests were performed with sodium citrate as anticoagulant. Wherever possible, also, hemoglobin and red cell determinations were carried out simultaneously with the sedimentation tests.

Results. In Tables 1 and 2 the readings at ½- and 1-hour periods are presented. The close correspondence in the results with the capillary and venous blood is at once apparent. As noted, in 45 tests with the blood of normal children ranging in age from

12 days to 14 years, the average sedimentation rate at the end of ½ hour was 4.3 mm. with the micromethod and 3.9 mm. with the macromethod. At the end of 1 hour the rate was 9.1 mm. with the former and 8.6 mm. with the latter. The 1-hour values fell within the range usually stated for the Cutler venipuncture method for normal adults. When the results of 27 additional microsedimentation tests with the blood of normal children were averaged with the 45 tests already noted, the rate for the finger-blood method for ½ hour was 4.2 mm. and for 1 hour 9.1 mm., with respective ranges of 1 to 8 mm. and 3 to 13 mm.

In 57 tests of the pathologic group with children of a similar age distribution, the average reading for the ½-hour period was 15.1 mm. with the micromethod as compared with 14.6 mm. with the macromethod. At the end of 1 hour the sedimentation rate with the former method was 20.8 mm. as compared with 20.6 mm. for the latter. The rates were slightly more rapid with the use of the microtube. It is significant, however that the differences were slight. The tendency of the 5% sodium citrate solution acting as an anticoagulant for finger blood to produce a slightly slower sedimentation rate than that with the weaker solution used for venous blood is counteracted by the more rapid settling of erythrocytes that occurs within the narrower microtube than in the wider Cutler tube.

Van Antwerp's observation[10] that successive sedimentation tests in children were subject to wide variations without apparent cause was not borne out in the present study. It will be noted in Table 1 that in the 3 children with whose blood, tests were repeated at intervals ranging from 5 to 9 days, the rates obtained were almost identical. In 8 additional instances with the blood of normal children not included in this table, successive microsedimentation tests carried out over a period from 2 days to 2 months revealed a maximum difference at the end of 30 minutes and 1 hour of 3 mm., this usually following the longest time intervals. In 26 determinations with the blood of sick children, repetition of the test within a period of a week, yielded surprisingly similar results unless the condition had undergone obvious clinical alteration. In this group the average difference in rates obtained in successive tests was less than 2 mm. in ½ hour and less than 1 mm. in 1 hour, the most uniform results being observed at the latter reading. In many instances duplicate estimations were carried out with successive specimens of blood from the same finger prick, with resulting readings that varied within a fraction of a millimeter. The discrepancies noted by Van Antwerp may possibly be accounted for by variations in the cell volume in repeated determinations or by changes in the status of the patient not in evidence clinically. Exact agreement between sedimentation rates even in the normal individual over intervals of 24 hours or more cannot always be expected. While progressive cellular destruction is expressed in

the wider fluctuations with which erythrocytes settle out of plasma, minor variations may reflect subtler aberrations in the ordinary physiologic mechanisms.

The close agreement in the rates of consecutive estimations emphasizes the reliability of the microsedimentation tests described in this study. In Table 2 a summary of the comparative sedimentation tests are presented in which the influence of heparin and sodium citrate are contrasted. The more rapid settling that occurs with heparin confirms the observations of Rourke and Plass,[7] who found that this substance does not affect the sedimentation of erythrocytes, whereas solutions of the inorganic anticoagulants serve to slow the reaction. For the relatively short tubes employed in this study, sodium citrate is preferable to heparin, since the greater distances traversed by the red cells of blood treated with the latter substance cause confusion at times in the interpretation of results in the case of normal individuals. Heparin constitutes an ideal anticoagulant, however, for use with longer sedimentation tubes where the larger sedimented layers are more readily comparable.

A fundamental consideration in the evaluation of the test is the influence of the concentration of hemoglobin, erythrocytes and the cell volume percentage of the latter upon the sedimentation rate. That an inverse ratio exists between the rate of settling of the cells and their number has been pointed out by many investigators. The more rapid rate of settling in a blood with fewer red cells is exemplified in instances of individuals with anemia whose sedimentation rates are comparable to those of patients with severe infections but who possess a normal complement of erythrocytes. Since the test was designed to indicate the degree of existing infection and tissue damage, attention has been directed toward means of correcting the sedimentation rate for fluctuations in the content of erythrocytes. The many procedures that have been proposed have for their purpose the transposition of the final sedimentation rate in terms of blood containing either a normal number[5] or a normal volume percentage of erythrocytes.[6, 9]

The methods range from a preliminary adjustment of the blood sample so as to obtain a red cell count of 5,000,000 per c.mm.,[5] to the correction with the aid of a chart for a normal cell volume after recording the rate of settling during short intervals so as to determine the period at which it takes place most rapidly.[9] Wintrobe and Landsberg's method[6] is simplified in that a single reading at the end of 1 hour is corrected for a normal volume of packed red cells.

While it is doubtless true that the correction for the concentration and volume percentage of erythrocytes is justified because it eliminates an important factor leading to equivocal interpretation, nevertheless objections have been raised at attempts for refinements

of the test. In the first place, a moderate reduction of the red cells is a frequent accompaniment of most infectious processes. Since these two factors move in close association throughout the course of an illness, it has been emphasized[11] that the uncorrected sedimentation rate constitutes an accurate index of the stage of pathologic activity and clinical status of the patient. This is true in the majority of instances, although it is not uncommon for the anemia to outrun the infection.

In addition, methods for correction are usually not interchangeable because of the lack of uniformity of sedimentation tubes, anticoagulants and technique. Wintrobe and Landsberg,[6] for example, showed that sedimentation proceeded more rapidly in a longer tube than in the shorter one. Thus, the red cells settle more rapidly in the 100-mm. tubes employed by Rourke and Ernstene,[9] and Wintrobe[4] than in the 50-mm. Cutler tube or in the one described in this paper. It is usually necessary, therefore, to determine a method for correction adapted for each type of test. Hubbard and Geiger[12] have also pointed out the difficulty of establishing an average normal sedimentation rate to serve as a basis for comparison because of the differences that exist in the speed of settling in blood specimens whose cellular constituents are numerically identical. The test, furthermore, finds its greatest usefulness not in the information derived from a single determination but by periodic repetition when it serves as a guide to the progress of infection. Fluctuations in erythrocytic content during short intervals are usually not sufficiently pronounced to alter the sedimentation rate as are the changes in the pathologic condition. Because of these considerations, many writers maintain that the sedimentation test serves its best purpose as a laboratory procedure simple of performance, and that correction only limits its availability for routine clinical use.

The drawback of introducing refinements which complicate the test cannot be denied. As a practical measure, however, it would seem best to carry out the test according to a prescribed method, but whenever possible to take cognizance of the erythrocyte content of the blood, especially where the rate departs markedly from the normal. This information may be obtained by determining the red cell count or the relative cell volume of the blood at the time of the test. Of the two, the estimation of the cell volume percentage is more significant, since this constitutes a combined measurement of the number of cells together with their size.

In the course of this investigation, it appeared important to compare the cell volume percentages in the normal with those of the pathologic group at the time of the sedimentation tests. The object was to observe to what extent anemia was associated with infection. The pathologic conditions were the common ones occurring in children and included in the main rheumatic disease, pneumonia,

childhood tuberculosis and upper respiratory infections. Blood dyscrasias were excluded.

As already stated, sedimentation tests were carried out not alone with 5% sodium citrate solution recommended for the microsedimentation tube described in this study, but also with heparin as anticoagulant. The reason for the higher volume percentage of packed cells with heparinized blood than with the sample treated with citrate has already been discussed. It may be noted in Table 3 that the packed cell volume in the group of normal children ranged from 36 to 49% in the heparinized blood and from 30 to 40% in the citrated blood. In the pathologic group the limits were 31.5 to 48% with heparinized blood and 26 to 42% with the citrated blood. In the pathologic group a hematocrit value of 36% and

TABLE 3.—SUMMARY OF CELL VOLUME PERCENTAGES.

Age.	No. cases.	No. tests.	Anticoagulant.			
			Heparin, %.		5% sodium citrate, %.	
			Average.	Extremes.	Average.	Extremes.
1. *Normal Group.*						
11 mos.*–14 yrs.	54	68	43	36.0–49	35.8	30–40
2. *Pathologic Group.*						
11 mos.*–13½ yrs.	66	162	41	31.5–48	33.5	26–42

* The observations below this age level were few in number and were omitted to facilitate comparison between the two groups.

over (lower level of the normal group) occurred in 93.8% of the heparinized blood specimens, and a value of 30% and over (lower level of the normal group) in 95% of the citrated bloods. It appears, therefore, that in the small unselected group of children with a variety of disease conditions, the erythrocytic concentrations as judged by the cell volume fell in the majority of instances within the range observed in the comparable normal group. Of course, the extremes for each group are subject to the modifications of larger series of cases and with the inclusion of more prolonged and a greater variety of infections.

The diversity of normal standards for cell volume percentages reported in the literature has added to the difficulty of designating an arbitrary value in terms of which correction is to be effected. The differences arise from the use of anticoagulants that cause changes in the osmotic pressure of the blood, the element of dilution, and the variation of the time and speed of centrifugation. In a recent investigation, for example, Osgood and Baker[13] found with the use of oxalated venous blood that the cell volume percentage in 215 tests in normal children, between the ages of 4 and 13 years, ranged between 28.76 to 46.51%, with an average of 36 cc. of packed cells

per 100 cc. of blood. With their method a correction of 3.5% of the volume of packed cells was necessary because of shrinkage due to the use of oxalate as anticoagulant. Centrifugation was carried out by them at over 4500 revolutions per minute,[14] until the cell volume remained constant. From the normal group reported in the present study, 43.5 cc. was the average cell volume per 100 cc. of blood of 51 tests in children of a similar age group. This value was obtained with heparinized blood after the specimens were centrifuged at an average time and speed of 30 minutes at 2500 revolutions per minute. Since heparin does not disturb the osmotic relations of the blood, no correction for shrinkage was necessary. This value corresponds to the hematocrit reading of 43.7 cc. of packed red cells per 100 cc. of blood for adults obtained by Haden[15] with the use of an isotonic solution of sodium oxalate.

Millar[16] and Ponder and Saslow,[17] in appraising the hematocrit method as a means of cell volume measurement questioned its accuracy because of the difficulty of deciding upon the end point. The hematocrit remains, however, the most practical instrument available for this type of determination and is thoroughly reliable for comparative purposes provided the technique is unchanged. Although the complete removal of fluid between the erythrocytes is desirable, it is possible that in obtaining this objective, changes may be induced by compressive forces upon the blood of individuals of various age groups especially when coagulation is inhibited through the medium of substances that induce shrinkage. Haden[18] found that at a speed of 2500 revolutions per minute the volume of cells after ½ hour centrifugation was only 2% greater than after 2 hours. The time and speed of centrifugation followed in the present study yielded results that differed to a slight degree only with those at higher speeds. In a small series of comparative estimations the cell volume with heparinized and citrated blood obtained after centrifuging at the standard speed of 2500 revolutions per minute for ½ hour exceeded by only 1% as a maximum the values obtained after centrifuging at a speed of 4000 revolutions per minute for ½ hour to 45 minutes. Because of the possibility of undesirable alterations with the blood of young individuals, the lower speed was adhered to.

In conclusion, it may be stated that the significance of an isolated, uncorrected sedimentation rate of a patient with an infection taken apart from a series, increases when the cell volume percentage falls within the range of normal, and that it may be accepted without reservation when it approximates the average figure. With the method described in this paper, and until larger series of observations are reported, the lower level of cell volume for citrated blood specimens may be regarded as 30% and the average as 36%. Comparison with these values is only essential when marked deviations from the normal rate of settling are noted in an initial test or with the occurrence of a sudden and unexpected shift in the course of

consecutive tests. Where facilities are available for centrifugation at the requisite speed, however, it would be desirable to determine and record the cell volume percentage together with the sedimentation rate. Such conjoint measurements are helpful in the final evaluation of the test, and when obtained periodically provide useful information in regard to the clinical and hematologic progress of the patient.

Summary. A method of determining the sedimentation rate of erythrocytes has been presented which employs capillary blood and is suitable for use with infants and children.

The tube that has been devised constitutes in effect a reduced macrosedimentation tube in that it embodies the basic requirements of apparatus in which sedimentation tests are carried out with venous blood.

Close agreement was noted in 102 comparative determinations with the method, in addition to 128 other microsedimentation tests, using blood from the heel of the young infant or finger of the older child and with a standard test utilizing venous blood.

With the microsedimentation method described in this study in which 5% sodium citrate was employed as anticoagulant, the average rate of settling in normal infants and children was 4.2 mm. for ½-hour and 9.1 mm. for 1 hour, with respective ranges of 1 to 8 mm. and 3 to 13 mm. The single determination at the end of 1 hour was sufficient for comparative purposes.

At the conclusion of the sedimentation test, the tubes were centrifuged for ½ hour at a speed of 2500 revolutions per minute. The range of cell volume in the normal group was 30 to 40% for citrated blood (average, 35.8%).

In a small group of infants and children with various infections, 95% showed cell volumes of 30% for citrated blood (lower level of the normal group) and over. This minimal value is tentative and may require modification with more extensive investigation.

Since the determination of the sedimentation rate has been applied chiefly as a guide to infection, various procedures have been devised to correct for the factor of anemia which in itself markedly influences the rate. While these methods are valuable, they are subject to the criticism that the test is thereby complicated and its availability for routine clinical use limited. It has, furthermore, been emphasized that moderate grades of anemia cannot be dissociated from infection and that they usually fluctuate together.

In the light of these objections and of others that are discussed, it is suggested that wherever possible the cell volume percentage be reported together with the sedimentation rate. The rate of settling may then be evaluated in accordance with the extent to which the cell volume percentage approximates the range of normal, instead of substituting for it a value derived by comparison with an arbitrary standard.

Since this paper was submitted for publication a large number of microsedimentation tests have been carried out and on the basis of this additional experience several technical details require reiteration. In the first place, the finger puncture must be adequate to insure a free flow of blood so that the complete specimen may be quickly obtained. Secondly, sufficient anticoagulant must be employed to prevent clotting of the blood from all types of pathologic conditions. To make certain of this, thorough preliminary rinsing of the pipette with the 5% sodium citrate should be effected and care should be exercised to introduce at least 0.04 cc. of this solution into the collecting test tube. If the column of anticoagulant falls below the 0.04 cc. graduation, clotting may occur, whereas, if this amount is slightly exceeded, the sedimentation rate is not perceptibly influenced.

As an extension of the studies described in this paper, cell volumes were determined, using the microtube as a hematocrit in which the results with a mixture of oxalates (Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. and Clin. Med., **19**, 777, 1934) were compared with those using heparin. An oxalate solution of 0.04 cc. (1.5 gm. of ammonium oxalate and 1 gm. of potassium oxalate dissolved in 100 cc. of water) was drawn up in the pipette, expelled into a collecting test tube and allowed to dry. This was sufficient to prevent clotting of 0.3 to 0.4 cc. of finger blood. The volume of packed red cells obtained after centrifuging the oxalated blood closely approximated the values obtained with the heparinized blood and were usually identical. The sedimentation of red cells from the oxalated blood in the microtube, however, did not proceed as smoothly and with the same regularity as did heparinized or citrated blood. The microsedimentation tube may, therefore, be employed as a reliable hematocrit for determining the actual volume percentage of red cells with the substitution for heparin of the less expensive and more available mixture of oxalates.

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MACROCYTIC ANEMIA IN LIVER DISEASE, PARTICULARLY CIRRHOSIS.

OBSERVATIONS ON THE INCIDENCE, COURSE AND RETICULOCYTOSIS, WITH A CORRELATED STUDY OF THE GASTRIC ACIDITY*

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IN recent years, reports of the occurrence of macrocytosis or of macrocytic anemia in diseases of the liver, unassociated with hemorrhage, have appeared in the literature with increasing frequency. Prior to this, the finding of this characteristic of pernicious anemia, particularly in hepatic cirrhosis, was regarded as most unusual,[1] meriting brief if any comment in treatises on this subject, all emphasis being laid upon the anemia secondary to hemorrhage.

The earliest observation of the coexistence of macrocytosis with liver disease was made in 1883 by Gram,[2] who found the diameter of the erythrocyte increased in obstructive jaundice, catarrhal jaundice and in a case of cirrhosis. Limbeck[3] (1896) found the volume of the red cells increased in catarrhal jaundice, and Capps[4] (1903) observed a high volume index in 2 cases of carcinoma of the liver. Recently, Wintrobe and Shumacker[5] recorded 11 instances of macrocytosis, and collected from the literature 57 other cases of macrocytic anemia associated with different forms of cirrhosis. To their series, I am able to add at least 80 cases of liver disease with macrocytosis found in a subsequent survey of the literature.[2,3,4,6–20] As with rare exceptions,[5,6] the reports deal with single cases or with small groups, an investigation of the incidence, nature and course of these morphologic changes in a larger series of patients with liver disease was undertaken, a report of which constitutes the basis of this paper.

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Material. Observations were made upon 62 cases of acute, subacute and chronic hepatic disease, 48 of which were cirrhosis, 7 toxic hepatitis, 1 acute yellow atrophy, 3 carcinoma of the head of the pancreas and 3 metastatic carcinoma of the liver. In the selection of patients, only those in whom a diagnosis of liver disease could be made without equivocation were chosen. The necessity for adhering to such a rigid criterion is borne out by the paucity of necropsies and operations performed in this group, only 10 in all. In consequence, the majority of the cases represent advanced hepatic disease.

A few brief remarks about the clinical features of the cases of cirrhosis may assist in visualizing the type and extent of the disease: Of 45 patients diagnosed as portal cirrhosis, 41 were in the hypertrophic and 4 in the atrophic stage. In 3 other patients, hypertrophic biliary cirrhosis was found at operation. The liver edge in the hypertrophic group was distinctly hard, and averaged 8.1 cm. below the costal margin on inspiration, with the limits of variation being 2 to 14 cm. In 31 cases, the surface was smooth, and in the remaining 13, it was irregular and nodular. The spleen was slightly to moderately enlarged in 11 patients, and in another, it descended 7 cm. below the costal margin. Ascites was present in 31 individuals, and edema of the lower extremities in 22. A history of chronic alcoholism was elicited in 31 of the patients, and 9 of these presented the manifestations of delirium tremens either upon entry or while in the hospital. Of the 62 patients studied, intrahepatic jaundice of a greater or lesser degree, indicating considerable hepatic dysfunction, was observed in 40 instances (Tables 1, 2, 3 and 4).

Methods. Blood counts were made every 3 or 4 days during the period of hospitalization and at variable intervals thereafter. Counting chambers and pipettes certified by the U. S. Bureau of Standards were used, and hemoglobin estimations were made with a Sahli hemometer standardized so that 14.5 gm. was equivalent to 100% (Wintrobe).[21] Cell volumes were determined by the Wintrobe hematocrit.[21] To obviate any possibility of congestion in the forearm, the tourniquet was released immediately after insertion of the needle into the vein, and a few seconds were allowed to elapse prior to withdrawal of the blood. Reticulocyte counts were made from blood supravitally stained with brilliant cresyl blue. Wherever indicated, fragility tests were made in order to aid in differentiating acquired or familial hemolytic icterus. In all cases, the degree of bilirubinemia was measured by the icterus index.[22] To study the relationship, if any, between achlorhydria and this type of anemia, Ewald test meals were given wherever feasible, and to patients showing an anacidity by this method, 0.35 mg. of histamin was administered subcutaneously and a fractional gastric analysis was performed.

Results. *Hepatic Cirrhosis.* Of the 48 patients with cirrhosis (Tables 1 and 2), a macrocytosis was found in 43 instances, an incidence of 89.7%*. This is strikingly shown by the mean corpuscular volume, which ranged from 75.4 to 142.5 c. μ., the average being 110.8 c. μ. The extraordinarily high figure of 142.5 c. μ. was obtained in Patient 18, at a time when the reticulocytes numbered 18% of the total red blood cells, and, from the work of Persons,[23]

* Dr. A. C. Ivy, Professor of Physiology at Northwestern University, has written us in this regard. "Dr. Rosenberg, as well as I, was surprised in regard to the high incidences of macrocytosis observed. When this appeared to be true during the earlier stages of his work, his technique was investigated for faults, and none found. It was then thought that as the work progressed the percentage would decrease; but it did not."—EDITORS.

TABLE 1.—HYPERTROPHIC CIRRHOSIS.

Patient.	Age.	Duration of Symptoms.	Hb. gm. per 100 cc.	R.B.C. millions per c.mm.	Vol.* R.B.C. cc. per 100 cc.	C. V.* c. μ	C. H.* $\mu\mu$	C. H. C.* per cent.	Reticulocytes. per cent.	Icterus index.	Anacidity.
1	45	2 yrs.	7.8	2.35	25.0	106.4	33.2	31.2	1.9	38	+
2	62	1½ yrs.	10.3	3.01	31.2	103.7	34.2	33.0	0.7	25	0
3	50	6 mos.	8.0	1.67	22.2	133.0	48.0	36.0	1.7	58	
4	45	6 yrs.	13.6	3.78	42.5	112.6	36.0	32.0	0.1	140	
5	35	3 yrs.	13.1	3.75	45.4	121.0	34.8	28.7	0.2	6	
6	49	4 mos.	10.4	3.13	37.0	118.0	33.4	28.2	1.5	50	+
7	54	6 mos	13.2	3.95	40.7	102.4	33.2	32.4	0.1	6	0
8	52	5 mos.	10.0	2.69	29.6	110.0	37.0	34.0	1.6	20	
			2/5/35								
9	50	10 mos.	11.2	3.93	.....	.....	.....	.....	.....	23	0
			2/13/35								
			13.0	3.96	47.4	120.6	32.8	27.4	0.7		
			2/20/35								
			13.4	3.95							
10	52	4 yrs.	13.2	3.24	37.7	116.0	40.7	35.0	3.8	33	0
			1/19/35								
11	43	16 yrs.	11.2	4.05	.....	.....	.....	.....	.....	4	0
			2/15/35								
			14.5	4.21	52.6	125.0	34.4	27.6	1.8		
			5/1/35								
			14.5	5.26	53.0	100.8	27.6	27.4			
			7/12/35								
			15.2	4.49	47.4	105.6	33.9	32.1	1.5		
			12/6/34								
12	40	6 mos.	10.9	3.99	.....	.....	.....	.....	1.7	22	
			2/15/35								
			13.0	4.01	43.8	109.0	32.4	29.7	...	...	
			3/15/35								
			14.0	4.31	44.3	102.9	32.5	31.6	0.5		
			7/12/35								
			15.0	4.13	44.1	106.8	36.3	34.0	0.6		
13	47	8 yrs.	14.0	3.23	38.8	120.0	43.4	36.1	0.2	66	0
14	48	3 yrs.	12.4	3.89	42.8	110.0	31.9	29.0	0.8	4	0
			3/15/35								
15	42	2 mos.	13.8	3.75	42.4	113.0	36.8	32.5	0.9	6	0
			5/10/35								
			14.6	4.23	46.3	109.6	34.6	31.5			
16	50	2 mos.	12.8	3.14	35.8	114.4	42.4	35.8	0.8	34	+
17	34	1 mo.	9.5	3.24	34.0	104.8	29.3	28.0	3.5	25	0
			2/13/35								
18	39	1 yr.	12.4	2.66	32.5	122.0	46.6	38.1	2.6	115	0
			3/13/35								
			5.2	1.09	15.5	142.5	47.8	33.5	18.0	60	
			3/13/35								
19	63	3 yrs.	12.6	4.42	42.9	96.9	28.5	29.4	0.0	6	
			5/22/35								
			12.8	4.27	41.2	96.4	29.9	31.1	1.3		
			7/3/35								
			14.0	3.98	43.7	109.8	35.2	32.0	1.0		
20	38	5 mos.	11.8	4.07	34.5	84.7	29.0	34.2	1.3	28	0
21	34	6 yrs.	13.1	3.30	40.3	122.0	39.4	32.2	2.1	34	0
22	52	3 wks.	13.0	3.56	39.0	109.7	36.6	33.3	1.8	30	
23	44	?	11.4	3.10	35.7	115.2	36.8	32.0	3.0	6	0
24	47	4 yrs.	12.6	3.31	34.0	102.7	38.1	37.1	2.3	28	0
25	31	1 yr.	9.6	3.53	30.0	85.0	27.2	32.0	1.2	26	
26	45	1 yr.	13.2	4.97	40.0	80.4	26.5	33.0	1.9	4	
27	43	1 yr.	16.2	4.14	52.1	126.0	39.2	31.1	0.2	3	0
28	42	7 yrs.	11.2	2.18	28.1	128.6	51.3	39.9	7.0	60	0
29	44	6 mos.	8.4	3.28	24.7	75.4	25.6	34.0	2.4	24	0
30	43	2 mos.	9.8	2.39	28.3	118.6	41.0	34.6	5.3	94	
31	46	?	16.4	4.41	50.5	114.5	37.2	32.5	0.6	4	
			5/22/35								
32	60	2 mos.	14.2	4.21	39.1	92.8	33.7	36.3	0.6	26	0
			6/21/35								
			13.0	3.76	39.1	104.0	34.6	33.2	1.3		
33	38	7 mos.	12.6	3.30	36.0	109.1	38.2	35.0	2.6	5	+
34	43	2 wks.	9.4	2.48	28.3	114.0	37.8	33.2	2.1	26	+
35	50	3 mos.	12.6	3.71	36.5	98.4	34.0	34.5	1.1	9	+
36	52	3 wks.	13.4	2.96	36.5	123.2	45.2	36.7	1.8	18	+
37	46	?	11.8	3.88	37.8	97.5	30.5	31.5	0.7	7	0
38	26	3 mos.	13.2	3.59	36.2	101.0	36.8	36.5	1.4	4	0
39	36	2 mos.	8.0	1.75	23.9	136.6	45.7	33.5	3.1	22	0
40	43	2 mos.	11.4	3.41	37.8	110.8	33.4	30.2	0.9	6	+
41	58	3 mos.	13.4	2.78	33.0	118.9	48.3	40.6	0.4	155	0
42	40	6 mos.	10.4	2.02	26.4	130.4	51.4	39.4	1.3	90	+
43	47	?	14.4	3.63	40.8	112.4	39.7	35.3	3.2	90	
44	54	3 wks.	10.2	2.73	30.7	112.2	37.1	33.2	4.3	18	0

* Vol. R.B.C.—Volume of packed red blood cells in 100 cc. of blood.
C. V.—Mean corpuscular volume in cubic microns. Normal, 80 to 94 c. μ.
C. H.—Mean corpuscular hemoglobin in micromicrograms. Normal, 27 to 32 $\mu\mu$.
C. H. C.—Mean corpuscular hemoglobin concentration in per cent. Normal, 33 to 38%.
Only significant changes noted during the period of observation are recorded in the tables.

TABLE 2.—ATROPHIC PORTAL CIRRHOSIS.

Patient.	Age.	Duration of symptoms	Hb.	R.B.C.	Vol. R.B.C.	C. V.	C. H.	C. H. C.	Reticulocytes	Icterus index.	Anacidity.
			gm. per 100 cc.	millions per c.mm.	c.c. per 100 cc.	c. μ.	$\mu\mu$.	per cent.	per cent.		
45	57	3 wks.	11.8	3.48	36.9	106.0	34.0	32.0	1.6	18	+
			2/27/35								
46	68	4 mos.	12.2	4.80	43.6	90.7	25.4	28.0	0.1	5	0
			5/1/35								
			13.2	4.85	44.3	91.3	27.2	30.0			
			7/12/35								
			12.0	4.17	39.1	93.8	28.8	30.7	0.6		
47	60	3½ yrs.	10.8	3.13	32.5	103.8	34.5	33.2	1.7	3	0
48	50	3 wks.	14.5	4.00	42.0	105.0	36.3	34.5	1.2	6	+

TABLE 3.—TOXIC HEPATITIS.

Patient.	Hb.	R.B.C.	Vol. R.B.C.	C. V.	C. H.	C. H. C.	Reticulocytes	Icterus index.	Free HCl.	Duration of symptoms.
	gm. per 100 cc.	millions per c.mm.	cc. per 100 cc.	c. μ.	$\mu\mu$.	per cent.	per cent.			
49	16.2	4.73	49.0	103.5	34.2	33.1	0.3	42	38 (Ewald)	1 wk.
50	16.4	4.32	46.4	107.3	37.9	35.3	0.9	100	44 (Ewald)	2 wks.
	9/5/35									
51	13.9	4.08	44.0	107.8	34.0	31.6	0.8	40		12 days.
	9/20/35							Icterus		
	13.2	4.33	38.9	89.7	30.5	33.9	. .	deer.		
52	15.2	4.38	44.3	100.6	34.6	34.3	0.2	60	28 (Ewald)	2 wks.
53	15.0	4.36	43.9	100.7	34.4	34.2	1.5	150	24 (Ewald)	3 wks.
54	13.4	3.82	39.1	102.2	35.0	34.3	0.1	37	40 (Ewald)	1 wk.
55	14.8	4.35	46.3	106.4	34.0	32.0	0.2	66	32 (Ewald)	16 days.

TABLE 4.—OTHER FORMS OF LIVER DISEASE.

Patient.	Age.	Duration of symptoms	Hb.	R.B.C.	Vol. R.B.C.	C. V.	C. H.	C. H. C.	Reticulocytes	Icterus index.	Anacidity.	Diagnosis.
			gm. per 100 cc.	millions per c.mm.	cc. per 100 cc.	c. μ.	$\mu\mu$.	per cent.	per cent.			
56	39	2 mos.	12.5	3.95	44.6	111.5	31.3	28.3	1.2	180	0	Ca. pancreas (op)
57	54	2 mos.	12.6	3.25	34.3	105.4	38.7	36.7	0.1	107	0	Ca. pancreas.
58	43	3 mos.	12.6	3.37	32.2	95.4	37.3	39.1	1.7	125	0	Ca. pancreas (op)
59	50	3 mos.	11.2	2.76	34.8	126.0	40.6	32.2	1.3	55	0	Diffuse hepatic Ca.; cirrhosis(?)
60	56	6 wks.	10.7	3.16	32.7	103.5	33.9	32.7	3.6	90	0	Huge Ca. liver.
61	52	2 mos.	17.0	4.20	48.4	115.2	40.5	35.1	2.2	120	. .	Diffuse Ca. liver.
62	19	3 wks.	14.0	4.80	52.0	108.0	29.2	27.0	0.6	187	. .	Acute yellow atrophy (P.M.).

may be explained in part, at least, by this degree of reticulocytosis. Of the remaining patients, 4 (Nos. 20, 25, 26, 46) showed a normocytosis and 1 (No. 29) a microcytosis. Patient 32 exhibited a normocytic anemia on admission, but within 4 weeks and concomitant with a rapidly increasing degree of hepatic insufficiency, developed a definite macrocytosis (mean corpuscular volume, 104 c. μ). Although Patient 46 has presented a normocytic anemia to date, a distinct tendency toward the development of a macrocytic type is manifest.

The red blood cell counts were below normal[24] in all but one individual (Patient 26). In Patient 46, who showed a persistent macrocytosis, the erythrocyte counts were normal when he first came under observation, but more recent studies have revealed a slight hypocythemia. The lowest count recorded, 1.09 million per cu. mm., was noted in Patient 18, 1 week before exitus, whereas the highest, 4.97 million, was found in Patient 26, who presented the clinical picture of an early cirrhosis. The erythrocytes in this group averaged 3.26 million. In 2 patients, a spontaneous rise in the erythrocytic level was observed synchronously with an improvement in their general condition. Thus, in Patient 11, the red blood cell count rose from 4.05 to 5.26 million in $3\frac{1}{2}$ months, and was accompanied by a more rapid, earlier gain in hemoglobin, from 11.2 to 14.5 gm. per 100 cc. within 1 month. In Patient 15, the erythrocytes rose from 3.75 to 4.23 million in 2 months, whereas the gain in hemoglobin, from 13.8 to 14.6 gm. per 100 cc., may be considered within the normal limits of variation.

The hemoglobin content varied from 5.2 to 16.4 gm. per 100 cc. of blood, with a group average of 12.0 gm. Mean corpuscular hemoglobin values, as observed upon admission, disclosed an hyperchromia in 39 individuals, normochromia in 6 and hypochromia in 3. In subsequent studies, it was noted that Patient 46, with an initial hypochromia, had developed a normochromic anemia. Similarly, the anemia in Patient 19, formerly normochronic, had assumed an hyperchromic character. It is conceded that the accuracy of Sahli hemoglobin estimations is untrustworthy in the presence of moderate or marked bilirubinemia, for the serum discoloration *per se* leads to a high, factitious value. The results are significant, however, since by far the majority of the group showing hyperchromia had either a slight or no bilirubinemia. A spontaneous rise in hemoglobin ranging from 1.4 to 4.1 gm. per 100 cc. occurred in 4 patients (Nos. 9, 11, 12, 19), the largest increment being noted after 7 months of progressive subjective improvement.

Accompanying these remissive tendencies, there has been a decrease in the mean corpuscular volume in 3 patients (Nos. 11, 12, 15), but in none did it return to normal.

Toxic Hepatitis. In all of the 7 patients with acute toxic hepatitis, a macrocytosis was found (Table 3). The increase in the mean cor-

puscular volume was, on the whole, of less magnitude than that in the cirrhoses, the variation being from 100.6 to 107.8 c. μ. It is worthy of mention that in Patient 49 the macrocytosis was already present on the seventh day of illness, and in another (Patient 51), it had disappeared within 2 weeks after improvement set in, indicating the rapidity with which cell changes may take place. A mild anemia was present in 6 out of the 7 patients, and in the remaining one the red blood cell count was normal. The hemoglobin readings were uniformly normal, thus yielding abnormally high mean corpuscular hemoglobin values (hyperchromia). The latter figures, however, cannot be accepted without reservation, for the grade of bilirubinemia in these cases undoubtedly effected an over-estimation of the true hemoglobin content.

Other Forms of Liver Disease. A macrocytic anemia was found in each of the 3 patients with obstructive jaundice due to carcinoma of the head of the pancreas and in the 3 patients with extensive metastatic carcinoma of the liver (Table 4). In 5 of these patients, the mean corpuscular volume ranged between 95.4 and 115.2 c. μ, and the erythrocytes numbered more than 3 million per c.mm. Patient 59, who had a mean corpuscular volume of 126.0 c. μ and an erythrocyte count of 2.76 million, gave a remote history of long standing chronic alcoholism, and, in view of the extreme hardness of the liver, was also suspected of having an hepatic cirrhosis. Perhaps the combination with the latter disease accounts for the greater degree of macrocytosis.

Patient 62, with acute yellow atrophy, exhibited a definite macrocytosis (C. V. = 108 c. μ), with a normal erythrocyte count and a subnormal mean corpuscular hemoglobin concentration.

*Reticulocytosis.** A reticulocytosis varying from 1.1 to 18.0% and averaging 2.47%, was found in 39 out of the 62 patients. This would connote an active erythropoiesis in the majority of our patients. Indeed, Bleichroeder,[26] Eppinger,[27] Boros[28] and Fellinger and Klima[6] have reported the pathologic finding of red marrow in the long bones, particularly the femur, in some cases of cirrhosis without hemorrhage. No exact correlation between the number of reticulocytes and the severity of the anemia is apparent, although the highest percentages were encountered in 3 of the patients with the more advanced anemia (Nos. 18, 28, 30). It is noteworthy, further, that of 43 patients with icterus, 30 manifested a reticulocytosis.† In contrast, of the 19 individuals without icterus, a reticulocytosis was found in only 9. This has been noted before (Schiff),[29] and seems suggestive of a possible relationship between the bilirubinemia and the number of reticulocytes.

* Considerable diversity of opinion exists today concerning the normal percentage of reticulocytes in the peripheral blood.[25] For the method employed in this study, the general consensus is that 0–1% is normal.

† Fragility tests were normal.

Relationship of Achlorhydria to the Anemia. Since an achlorhydria in the presence of a macrocytic anemia may denote a deficiency of the "intrinsic factor" of Castle (Isaacs and Goldhamer[30]), it is of interest to study the incidence of its association with the macrocytic anemia in liver disease. In only 11 out of the 48 patients on whom the gastric acidity could be determined, was a true achlorhydria observed. Wintrobe and Shumacker[5] found an achlorhydria in 4 out of 10 patients, whereas Van Duyn[14] observed it in none of his 4 patients. It appears, therefore, that in hepatic disease no correlation exists between the absence of free hydrochloric acid and the development of a macrocytic anemia. Nor is the degree of macrocytosis any greater in those patients with achlorhydria. Wintrobe[5] has reported the presence of the "intrinsic factor," apparently in adequate amounts, in the gastric juice of a patient manifesting cirrhosis, macrocytic anemia and free hydrochloric acid, which is in accord with our conclusions.

Discussion. The finding of a macrocytosis, almost invariably associated with an anemia, in 89.7% of the patients with cirrhosis and in 91.9% of all the patients with various forms of hepatic disease, is in striking contrast with the incidence as recorded by other observers. Thus, in a study of 57 cases of portal cirrhosis without hemorrhage, King[31] found none with macrocytosis or with hyperchromic anemia. Wintrobe and Shumacker[5] reported a macrocytosis in 11 out of 43 patients (25%) with liver disease. Fellinger and Klima[6] noted an hyperchromic anemia in 18 out of 48 patients (37.5%) presenting various grades of cirrhosis, but they were of the opinion that practically all such cases, if followed long enough, would ultimately manifest an hyperchromic anemia. They advanced no conclusive evidence to substantiate their belief. In a recent experimental study of carbon tetrachlorid cirrhosis in rats, Higgins and Stasney[32] observed the progressive development of a macrocytic anemia, in which the macrocytosis and the anemia increased proportionately with the increase in the degree of cirrhosis. Since our patients presented indubitable clinical evidence of widespread liver disease, which in most instances was in an advanced stage, this factor alone would seem to afford an explanation of the higher frequency of macrocytic anemia in our series.

Although the "tendency" to develop a macrocytic anemia in hepatic disease has been noted by Wright,[13] the transition from a microcytic or normocytic anemia to a macrocytic type, as an accompaniment of increasing liver damage, has been observed by Goodhart,[9] Van Duyn[14] and by us (Patient 32). The further progressive increase in the degree of macrocytosis and anemia coincident with rapid liver destruction (Patients 18 and 32), together with the presence of the greatest macrocytosis in our patients with the most advanced anemias, or in the terminal stages of cirrhosis, provides clinical corroboration of the work of Higgins and Stasney,[32] and

completes a vivid picture of the evolution of the erythrocytic changes. As a corollary to this, it becomes apparent that either a progressive anemia in the absence of hemorrhage, or an increasing macrocytosis, may be utilized as a prognostic guide in chronic or advanced liver disease.

Spontaneous hematologic improvement occurring during the course of hepatic disease, as in Patients 9, 11, 12, 15 and 51, needs engage our interest. Wintrobe and Shumacker[5] observed improvement in 4 cases of chronic liver disease and during recovery from acute catarrhal jaundice. Similarly, Gram,[2] Meulengracht,[33] Stewart,[10] and Van Duyn[14] recorded remissions in patients recovering from widespread liver damage with intense jaundice. Hence, it is reasonable to infer, that with the regeneration of liver cells, a restitution of the normal hematopoietic function of the liver may be evoked.

The perplexity of a rising hemoglobin in the face of continued liver destruction, as noted by us (Patient 9) and by others,[5] remains unsolved. Since our patient presented a bilirubinemia (icterus index, 23), consideration of the clinical evidence favoring the formation of hemoglobin from bile pigment (Patek and Minot[34]) suggests the possibility of hemoglobin regeneration evolving from the excess circulating bile pigment. Our finding of a reticulocytosis with greater frequency in patients with jaundice seems to offer sustaining evidence in this direction.

The failure in the past to recognize macrocytosis as a frequent concomitant of widespread liver disease may be satisfactorily explained. The inadequacy of cell diameter measurements and of Price-Jones frequency curves on the blood of patients with an erythrocyte count in excess of 3 million per c.mm. has already been emphasized by Haden[35] and by Wintrobe,[21] for results may be obtained which deviate so little from normal, that they possess very limited if any diagnostic value. That the average erythrocyte count for our series was 3.42 million per c.mm. bears recapitulation at this point. Further, measurements of the cell diameter do not take into account the three dimensional variations in size, a fact best illustrated by Haden's[36] cogent observation: "An average increase of 1 micron in the diameter of an erythrocyte increases the volume 44% if the thickness is increased in the same ratio." From the blood smears of our cases, the cells appeared to be slightly enlarged but quite uniform in size when the red cell count was greater than 3.5 million per c.mm., only an occasional outstanding macrocyte being seen in some cases. In the more advanced anemias, a conspicuous macrocytosis, slight or moderate anisocytosis, a relatively slight poikilocytosis and, in some, an occasional microcyte were in evidence. Routine examination of a blood smear may, therefore, fail to reveal any macrocytosis in the average case. By the use of an hematocrit, it is likely that a macrocytosis will be

found in liver disease, more particularly in the advanced forms, with much greater frequency than heretofore.

Several hypotheses have been propounded in explanation of the origin of the macrocytosis and anemia. Naegeli[37] and Holler and Kudelka[17] thought the anemia was due to an endogenous toxic effect upon the red blood cells. Meulengracht[33] believed the macrocytosis to be dependent upon alterations in the blood plasma, resulting in a swelling of the cells. His observation that the diameter of the erythrocytes varied directly with the intensity of the icterus, as well as the lack of evidence in his cases pointing to a new formation of red blood cells, favored his belief. He felt that possibly the bile acids were responsible for this change. Capps, at an earlier period, had entertained this hypothesis, but rejected it on the grounds that simple swelling of red cells could not account for the high color index. He concluded that a macrocyte rich in hemoglobin must result from abnormal cell development, not from simple osmosis. It is apparent from our studies that the occurrence of macrocytosis in the absence of icterus, and its persistence in some cases long after the icterus disappeared, together with the evidence of erythropoiesis (reticulocytosis) in many patients, are at variance with the above observations of Meulengracht, and tend further to refute his hypothesis as the sole explanation.

Perrin[38] regarded the anemia as secondary to hepatic insufficiency, and administered liver to his patients with apparent subjective and hematologic improvement. More recently, Boros[11] concurred in this view, and believed that the secondary, increased erythropoiesis introduced many macrocytes into the blood.

Castle and his coworkers[39] have pointed out that the common factor in the production of macrocytic anemia is the failure of a specific reaction between the "extrinsic factor," present in food, and the "intrinsic" gastric factor; in many, the combination of a gastric defect and partial dietary deficiency appears to produce the same effect as the total absence of either factor. Failure to absorb or utilize the hematopoietic product of this interaction* may produce a similar effect. That this active substance is stored in the liver was first demonstrated by Ivy, Richter and Kim.[40] Hence, an extensively damaged liver, being incapable of storing sufficient amounts of the hematopoietic principle, might be accompanied by a macrocytic anemia.[15,19,29] Goldhamer, Isaacs and Sturgis[19] have corroborated the work of Ivy *et al.*, and have found the active substance either reduced or absent in hepatic cirrhosis with macrocytic anemia. In a case of acute yellow atrophy with macrocytic anemia, they found that the active principle, although present in the liver, apparently was not utilized by the body. Whipple and Robscheit-

* The work of E. A. Greenspon (J. Am. Med. Assn., **106**, 266, 1936) seems to indicate that the hematopoietic principle is normally elaborated and secreted by the gastric mucosa, an "extrinsic" factor being unnecessary.

Robbins,[41] studying the hemoglobin production factors in the human liver, observed the lowest values in cases of severe liver injury with anemia. Thus, the view of a deficient storage or utilization of the active hematopoietic principle by a defective liver seems at present to be the most tenable explanation of the macrocytic anemias in liver disease.

In evaluating the cause of the anemias in our cases, cognizance must be taken of the possible rôle of chronic alcoholism, a history of which was elicited in 65% of the patients with cirrhosis. The resultant dietary deficiency noted in 6 patients with macrocytic anemia, as manifested by polyneuritis,[42] or glossitis,[43] or both, is of singular importance, and probably contributed in no small measure to the development of the anemias. Eliminating these 6 cases, the incidence of macrocytosis is approximately the same (91%). In view of the frequency of chronic gastritis attendant upon chronic alcoholism, perhaps in some of the cirrhoses the combination of a gastric defect and mild dietary deficiency might have been provocative of a macrocytic anemia. This is not ascertainable from the data at hand, but if these cases too are excluded from consideration, the incidence of macrocytosis among the remaining 30 patients with widespread or advanced liver disease is approximately 87%. Excepting the cases of manifest dietary deficiency, it would appear that, for the most part, factors other than hepatic insufficiency played a relatively insignificant rôle in our series.

The possibility of the macrocytosis having been due in some cases to acidosis deserves consideration. Although the carbon dioxid combining power of the bloods was not determined, clinical evidence of acidosis was absent and urine examinations were normal.

It may be of interest to direct attention to the subnormal mean corpuscular hemoglobin concentrations* found in 20 cases with macrocytosis. In 1 of these, the value has gradually risen to normal; in 3, although it has increased, the value is still subnormal. In 6 of this group, hyperchromia was not present. From these results, one might speculate that the chronologic sequence of the cell changes consists of a more or less transitory swelling of red blood cells, followed by an elevation in the hemoglobin to a normal or hyperchromic level and, as a result of an insufficient amount of hematopoietic substance, by the subsequent appearance of true macrocytes. The initial increase in cell volume might result from a lowered colloid osmotic pressure secondary to the decrease in the serum albumin fraction,[44] so frequently found in hepatic insufficiency, or in advanced hepatic disease.[45] Such an hypothesis gives prominence to Meulengracht's original idea, but only in a restricted sense. Further studies, however, are essential for a better understanding of these blood changes.

* Values greater than 32% were considered normal.

The treatment of this anemia by parenteral liver extract has, in most cases, been disappointing.[5, 6, 9, 46] Only in several instances have satisfactory results been attained.[5, 9, 19, 22] Of 5 patients treated intensively with a potent extract, none showed hematologic improvement, although in 2 a slight reticulocyte rise occurred. It seems likely that the liver is essential for the intermediary metabolism of liver extract, converting it into an effective hematopoietic substance. In this way, we may account for the varied results following liver therapy in patients with hepatic disease, little or no response being elicited in cases with extensive liver damage.

Summary. 1. The morphologic changes in the blood of 62 patients with various forms of widespread or advanced hepatic disease are recorded.

2. Either a macrocytic anemia or macrocytosis alone was found in 91% of the patients.

3. Spontaneous hematologic improvement may occur in the course of acute or chronic hepatic disease.

4. Clinical evidence pointing to a relationship between the degree of macrocytosis and anemia and the extent of hepatic insufficiency is presented, and its prognostic significance is indicated.

5. A reticulocytosis occurred in 39 patients and was more common with bilirubinemia. The implications are discussed.

6. Achlorhydria is not essential for the development of macrocytic anemia in liver disease.

7. Macrocytosis in liver disease may possibly result from a primary swelling of the erythrocytes, followed by the secondary appearance of true macrocytes.

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ANEURYSM OF THE ABDOMINAL AORTA: A STUDY OF 73 CASES.

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Following experience with several cases of aneurysm of the abdominal aorta, it was thought desirable to study all such cases admitted to the wards of Charity Hospital in the past 30 years. All authors discussing the condition point out the infrequency of such aneurysms. Because of the high rate of syphilis among the negroes admitted to this hospital, it offers an ideal place to collect a group of cases.*

* Since this paper was written, there have been 4 additional cases: 1, a colored female, aged 38, presenting erosion of vertebræ upon roentgen ray study; 2 males, 1 white, aged 53, and 1 colored, aged 38, died from rupture of the sac, proved at necropsy. Another, a colored male, aged 51, was studied on the author's ward; he presented pulsation in the left paravertebral region, a palpable mass, and by the roentgen ray erosion of the last two dorsal, and first lumbar vertebræ as well as the twelfth rib. These 4 cases, with the 1 mentioned in the section on diagnosis and not included in the statistics, brings the total number of cases to 73.

This paper is based on a study of 68 cases of abdominal aneurysm. All but 3 arose from the abdominal aorta. Three arising from the celiac axis were included, for they could not be differentiated from the others except at necropsy. Cases were chosen for consideration only when good evidence was available to make the diagnosis a certainty. Thus the diagnosis was proven at necropsy in over one-half the cases. In the others the roentgenologic and physical features were considered sufficient. Exploratory laparotomy made the diagnosis in 2 cases. A number, equal to almost one-half the accepted cases, were discarded because of lack of data substantiating the diagnosis of aneurysm of the abdominal aorta.

Incidence. Aneurysm of the abdominal aorta is encountered infrequently in anyone's clinical experience. No extensive collection of cases has been made since Nixon's appeared in 1911.

Bryant,[1] in 1903, reported the necropsy cases showing this lesion at Guy's Hospital from 1854 to 1900. During this period in 18,678 autopsies there were 325 aneurysms of the aorta, of which 54 (16%) were of the abdominal aorta.

In 1905, Osler[2] reported 16 cases which had been found in 16 years among 18,000 ward admissions at Johns Hopkins Hospital, an incidence of 1 abdominal aneurysm to 10 thoracic aneurysms. In the first 200 necropsies at that institution there had been 49 aneurysms of the thoracic aorta and 11 of the abdominal aorta. This author called attention to variation in incidence in various localities, pointing out that in a series from Vienna there had been 3 abdominal aneurysms in 222 aortic aneurysms found in 19,300 autopsies.

In a monograph not available to me, Nunneley reported 32 cases of abdominal aortic aneurysms which occurred among 17,872 autopsies done at St. George's Hospital over a period of 65 years. These are included in Nixon's series which follows:

Nixon,[3] in reporting a case of aneurysm of the abdominal aorta due to congenital syphilis in a girl, aged 20, collected 233 cases.

In 1918, Marlow and Doubler[4] reported a case of abdominal aortic aneurysm with rupture into the duodenum. At this time they collected 11 more cases of abdominal aneurysm reported since Nixon's paper, bringing the total to 244 cases. Of this whole group, they had been able to find only 5 cases with rupture into the gastrointestinal tract.

From this last paper to the present date I have been able to find reports of 69 more cases, all of which have appeared as single case reports, except for a few. Gernert[5] published 6 instances of abdominal aneurysm found among 28 aortic aneurysms in 1062 autopsies. Dafoe[6] reported 2 cases of ruptured abdominal aneurysms due to tuberculosis, the diagnosis being established microscopically. Farmer,[7] in describing bone absorption in the spine due to abdominal aneurysm, reported 3 cases.

Thus, up to the time of the writing of the present paper, there have been reported, in the literature, about 313 cases of abdominal aneurysm. This paper adds 68, bringing the total to 381 cases. Among these have been 9 cases with rupture into the gastro-intestinal tract to which this paper adds another, a case with rupture into the stomach.

The 68 acceptable cases considered in this paper were found at Charity Hospital over a 30-year period, in which time there were 215,516 medical admissions. Of this series, 38 were proven at autopsy, in a total of 12,053 necropsies during this time. During the 30-year period the diagnosis of aortic aneurysm was made 976 times. In a recent study the author made of these, 532 were accepted as cases of unquestionable aneurysm. Considering then, undoubted cases, the incidence of abdominal aneurysm is 1 to 7.8 cases of thoracic aneurysm.

Etiologic Factors. *Race.* As was to be expected, the greatest number of aneurysms occurred among the negroes. Not that that race in itself is a major factor—though I am inclined to believe in a greater tendency to vascular disease in the colored person—but because of the higher incidence of syphilis. Fifty-four (79.4%) were negroes, whereas 14 (20.5%) were whites.

Sex. Because of the specific etiology of aneurysm, and possible effect of physical labor, the frequency of aneurysm of the abdominal aorta would be expected to be greater among the males. Thus 57 (83.7%) of the patients were males. Nixon, in his 233 collected cases, found 207 (88.8%) to be in males and 26 (11.2%) in females.

Occupation. This was recorded in 50 cases; 44 of these did physical work. Most were common laborers, but others whose work was manual were farmers, sailors, mechanics and carpenters. Among the women were 5 whose occupation was heavy housework and 1 that of a dressmaker.

TABLE 1.—DISTRIBUTION AS TO AGE, SEX AND COLOR.

Age in years	Colored males.	White males.	Colored females.	White females.
20 to 24	3	..	3	
25 to 34	8	5	3	
35 to 44	20	2	2	
45 to 54	9	3	..	1
55 to 64	4	1	..	2
65 and up	1			
No age given	1			
Total	46	11	8	3

Age. Aneurysm is usually considered to be a disease of the fourth and fifth decades. In this group, 6 patients, all colored, were found to be between 20 and 25 years; 22 (32.3%) were under 35 at the time of admission to the hospital; 46 (67.6%) were under 45. Table 1 indicates the distribution of cases as to age, sex and race.

Syphilis. The Treponema pallida is undoubtedly the most frequent specific agent in the production of aneurysm. The Wassermann reaction is naturally not necessarily positive in syphilis. The test was carried out in 39 cases and not recorded in 29 cases. Of the 39 recorded reactions, 19 (48.7%) were positive and the balance negative. A history of penile sore was obtained in 28 cases. Of these, 8 presented a positive Wassermann reaction, 12 a negative and in 8 no record of a blood Wassermann was available. (Antisyphilitic treatment had been administered in 11 cases, of which 6 showed a negative Wassermann test.) If we add the 20 cases in which the history of a penile sore was obtained, but in whom the Wassermann reaction was either negative or not recorded, to the 19 cases in whom a positive reaction was obtained, we have as evidence of syphilis either a history of chancre or a positive Wassermann reaction in 39 cases (57.3%). Unfortunately it is only in recent years that the necropsy protocols describe microscopic examination of lesions. Therefore, microscopic evidence of syphilis appears in only 5 cases of the 38 that came to necropsy. In an additional 9 cases the gross lesions of the aorta were described as being syphilitic.

Arteriosclerosis. It is accepted that with marked atheromatous changes of the aorta, as are seen in older age groups, aneurysm of the aorta may occur. Kampmeier and White[8] reported such a case in which the most extreme atheroma of the aorta was present. They reported this case because of the association of a dissecting aneurysm of the descending arch with an aneurysm of the abdominal aorta. It is possible that in a very few of this group, aneurysm may have originated on the basis of atheroma. Only 8 were above 55 years and only 1 above 65.

Tuberculosis. This etiologic factor has been described by Dafoe.[6] He reported the only 2 such cases in which tubercles were demonstrable microscopically. In the literature this author was able to find only 11 cases of aortic aneurysm due to tuberculosis, all of them being of the thoracic segments. Tuberculosis may cause aneurysm by involvement of the intima, by lesions of the media or adventitia, though infection *via* vasa vasorum, or lastly by extension from tuberculous lymph nodes, abscess or bone lesion. (We have seen 1 case of aneurysm of the aortic arch due to extension from tuberculous lymph nodes.)

Trauma. Crushing injury to the abdomen, with probably interruption of the integrity of the aortic wall, has been rarely described as a cause of aneurysm of the abdominal aorta. Apparently none of the cases in this series presented the etiologic factors which would place them into either of these last two classes.

Symptomatology. Eight cases were admitted to the hospital either practically moribund, or died so soon after that no history was obtained.

Pain was the most frequent symptom, being present in 55 (91.6%) of the 60 cases giving a history. It made up the admitting complaint in almost this number. The pain was remarkable in its wide distribution. However, in most cases the pain was referred to one of several sites. Most frequently the pain was localized to the abdomen, namely, in 32 patients. Of these, 10 specifically named the epigastrium as the site, 1, the left lower quadrant, and 3, the left side of the abdomen.

The next most frequent site of pain was the back. In 20, pain was present in this region distributed as follows: 11 patients localized the pain to the middle of the back, 6 to the left lumbar region, 2 to the right sacroiliac area, and 1 to the lower back. One patient referred pain to the left hip and thigh, 1 to the left thigh and knee, and a third to the right thigh. In 1 patient pain was localized to the right chest, and in another to the precordial region. In some patients pain was referred to more than one site.

Radiation of the pain from the original sites as described above was generally downward. In 6 patients the pain was referred to the left lower extremity, to the thigh alone, or to the thigh and leg, and in one to the foot. In the thigh the inner and outer aspects were described as being affected. Radiation was to the right thigh in 3 cases. The left groin was the site of radiation in 2 and to both legs in 1. Unusual was pain radiating to the left shoulder in 2 cases. There was roentgenologic evidence of erosion of lumbar vertebræ in 10 of the cases in which radiation of pain was downward. Radiated pain was no doubt due to root involvement.

Pain was described as being constant in 21 of the 55 cases presenting pain. It was intermittent in character in 12. In the rest, no description was available. Several patients complained only of pain after meals. Among the group complaining of constant pain were some who described the pain as having been intermittent at first, but with the progress of the disease it had acquired the characteristic of being practically constant. Quite frequently statements were made that pain was especially worse at night, or that it was particularly aggravated when lying down.

The type of pain varied greatly, though the severity was stressed by most patients. Pain was often described as being throbbing, synchronous with the heart beat, in others it was like a knife thrust, or lancinating, in many it was said to be of an aching character. A few patients described the pain as being colicky in nature, and in others as stinging sensation; 22 stated the pain had been getting progressively worse, and only 1 admitted improvement in pain.

The presence of tumor, as recognized by the patient, was recorded 9 times; in 8 it was abdominal and in 1 the left flank. A mass had been noted for varying lengths of time, from 1 month, the shortest, to 2½ years, the longest. "Indigestion" occurred in 12 cases, nausea and vomiting in 7 of these at intervals. Difficulty in urina-

tion and dizziness were noted in 1 each. Loss of weight was complained of in 23 patients, the amount varying from a few pounds to as much as 35 pounds. In Table 2 are listed the symptoms which were found in this group of aneurysm cases.

TABLE 2.—SYMPTOMS IN 60 CASES.

Symptom.	No. cases.	Symptom.	No. cases.
Pain:		Pain:	
Abdomen, general	18	Lower extremities	3
Epigastric	10	Right chest	1
Left abdomen	3	Precordium	1
Left lower quadrant	1	Tumor mass	9
Middle back	11	"Indigestion"	12
Left lumbar	6	Vomiting	7
Right sacroiliac	2	Dysuria	1
Lower back	1	Loss of weight	23

Two patients gave no data in their histories which suggested abdominal disease, their story being that characteristic of cardiac failure. In a third patient the history was typically that of a carcinoma of the esophagus which was the cause of death as proven at necropsy, the abdominal aneurysm being coincidental.

The duration of symptoms is of interest. Cases of more than 1 year's duration were very few. In 57 cases, where the history of duration of symptoms was given, it was found that in 35 (61.3%) the symptoms were of 6 months' or less duration, and that in 51 (87.7%) the symptoms had been present no more than 1 year. Duration can best be considered in table form (Table 3):

TABLE 3.—DURATION OF SYMPTOMS IN 57 CASES.

Duration.	No. cases.	Duration.	No. cases.
1 wk. or less	5	9 to 12 mos.	12
1 to 4 wks.	2	12 to 18 "	2
1 to 3 mos.	12	18 to 24 "	1
3 to 6 "	16	2 to 3 yrs.	2
6 to 9 "	4	8 yrs. (questionable)	1

Physical Findings. Except for the abdomen, the physical examination in most of the patients did not reveal any remarkable findings. The few extraneous signs which were noted will be briefly enumerated after the abdominal findings have been described.

On inspection, fullness of the abdomen was noted usually of either the epigastric or of the left subcostal regions. These findings were recorded in 10 cases. Visible pulsation was noted in a few of these. In 3 cases the aneurysmal sac pointed posteriorly with visible tumor in the back. One of these presented a tumor the size of a grapefruit projecting to the left of the spine, having eroded the lowest 3 ribs on that side. The second similar case had a tumor described as the size of a fetal head, projecting 6 cm. above the level of the surface and located to the left of the spine from the tenth dorsal to the third lumbar vertebra. The third presented a mass the size of one-half cocoanut to the left of the spine and below

the ribs. Dilated veins over the abdomen were described in 4 cases and dilated veins over the right thigh in 1.

A tumor in the abdomen was described upon palpation in 47 (60.3%) of the cases. In 3, described above, where the sac pointed posteriorly, no mass was described in the abdomen, though examination may not have been as careful in the face of the obvious lesion. In the remaining 18 cases no tumor was described, though in 2 the abdomen was too rigid for satisfactory examination. Pulsation was described in 2 others, but no mass was noted. Site of the mass was most frequently found to be epigastric or in the left subcostal region. The tumor was epigastric in location in 24 (50%) of the 47 cases presenting abdominal tumor. In 10, it was at the left subcostal margin. The sac was found lower in the abdomen at the region of the umbilicus, though usually to the left of it in 8 cases, in 1 of which the tumor extended from the subcostal margin to the crest of the ilium. A mass in the left renal region was noted in 3 cases. In 2, the tumor was located in the right abdomen, 1 in the lower quadrant and 1 to the right of midline in the upper abdomen.

The description of the size of the tumor varied a great deal, terms of common objects being usually used to describe the size. The tumors were described as the size of a grapefruit, baseball and closed fist; 9 were said to be the size of an orange and 9 were merely described as being large; 4 varied from 7 to 15 cm. in diameter. In the balance of the cases no description of size was given.

In the 50 cases in which tumor was described, pulsation of the tumor mass was recorded in 49. Aside from the cases with the sac projecting posteriorly, 4 other cases in which the mass was felt anteriorly showed definite palpable or visible pulsation in the left lumbar region. Thirty-nine (79.6%) demonstrated an expansile type. A palpable thrill was present in 3 cases. A bruit, systolic in time, was heard over the sac in 26 (52%) of the cases of pulsating tumor. Tenderness on palpation of the mass was present in a high percentage of the cases, and in 6 tenderness was also noted in the left flank or left lumbar region. Rigidity of the abdomen on palpation was often found, especially on the left side.

The rest of the physical findings were more or less incidental. Lag and limited excursion of the left lung base occurred in a few cases. Impairment of the percussion note at the left base, distant or changed breath sounds, and râles were noted in an occasional case. A friction rub was heard at the left base in 2 cases. Cardiac enlargement was recorded in 14 cases. The murmur of aortic regurgitation was recognized twice. One patient presented neurologic disturbances of the left lower extremity due to pressure on the spinal roots.

Roentgenologic Findings. The roentgenologic examination has in more recent years been found to be of exceeding importance as an

aid in the diagnosis of suspected aneurysm of the abdominal aorta. This is clearly shown in the more recent half of this series of cases. The data which will be shown to be important criteria in diagnosis has been gathered from cases seen in the last 10 to 15 years at Charity Hospital.

The Roentgen ray was used in 32 (47%) of all cases for assistance in the specific diagnosis of abdominal aneurysm. In 3 cases it was used with other diagnoses in mind, namely, studies for renal calculus and gastro-intestinal disease, which were negative, and in 1 case of carcinoma of the esophagus.

The most important roentgenologic finding is that of pressure erosion of vertebræ. Studies of the spine were made in 24 of the 32 cases. In 18 of these (75%) erosion of the vertebræ was made manifest; 4 of this group also showed gastric displacement by the sac as well as erosion. In 6, studies of the spine were negative. Of the 8 cases in which the Roentgen ray was used in studies exclusive of those of the spine there were 5 in which fluoroscopic examination was used, showing in 4 a pulsating tumor, the fifth being negative. In 1 of the 4 was recorded gastric deformity by a pulsating mass. Of the remaining 3 cases in which the Roentgen ray was used as an aid, with abdominal aneurysm in mind, was 1 in which the shadow of the sac was obtained by use of pneumoperitoneum and 2 in which flat plates were used, 1 being positive and 1 negative. As a result we see that in 32 cases in which the Roentgen ray was used with the tentative diagnosis of abdominal aortic aneurysm, it gave a positive answer in 24 (75%) of cases. Calcium deposit in the wall of the sac was seen in 3 cases.

TABLE 4.—VERTEBRÆ ERODED IN 18 CASES.

	No. cases.		No. cases.
Dorsal, eleventh	2	Lumbar, second	8
Dorsal, twelfth	9	Lumbar, third	1
Lumbar, first	16		

Erosion of the vertebræ, being of such importance, should be described in a little more detail. In 2 cases there was erosion of 1 to 3 of the lower ribs as well as of the vertebræ. Of the 18 cases showing erosion, all but 3 presented involvement of 2 or more vertebræ. The most frequent combination was erosion of the twelfth dorsal and first lumbar vertebræ (Table 4). The erosion seen is characteristically of the anterior and left lateral aspects of the vertebral bodies. The intervertebral disks are not involved in this destruction (Fig. 1).

Diagnosis. From the records it was impossible to learn how frequently the correct diagnosis of abdominal aneurysm was made. But from the request blanks addressed to the Roentgen ray Department in recent years, it is evident that such a tentative diagnosis was made in a fairly high proportion of the cases. In

FIG. 1.—The arrow indicates erosion of the body of a vertebra as shown by the Roentgen ray.

FIG. 2.—Pressure erosion by aneurysm of the abdominal aorta, characteristically involving vertebral bodies, leaving intervertebral disks intact.

such, an abdominal tumor presenting expansile pulsation led to a diagnosis.

As every clinician knows, an abdominal tumor accompanied by pulsation is not uncommon. Ordinarily, the pulsation is merely transmitted from the aorta lying posterior or adjacent to the tumor, whatever its origin. However, if the examination permits the grasping of the tumor between the two hands, one on either side, and thus presents expansile pulsation, the diagnosis of abdominal aneurysm may justifiably be entertained. As was noted above, expansile pulsation was demonstrated in about 80% of 49 cases presenting tumor with pulsation. Confirmatory evidence is a systolic bruit heard over the tumor, and a palpable thrill. In the presence of a tumor with expansile pulsation, or any other tumor suspected for one or another reason of being an abdominal aneurysm, the Roentgen ray frequently offers evidence of greatest importance in arriving at or in confirming the diagnosis. Erosion of the lumbar vertebræ, especially without destruction of the intervertebral disks is practically pathognomonic of aneurysm. As was discussed above, these findings appeared in over one-half of the cases in which the Roentgen ray was used for its assistance in the diagnosis of this lesion. Since the abdominal aneurysm usually is due to syphilis, the Wassermann reaction may be of assistance, but we cannot place too much reliance on this feature in diagnosis. Early in the paper I discussed evidence of syphilis in this series. Further, due to the high incidence of syphilis among the negroes admitted to Charity Hospital, we must constantly consider other diseases coincident with syphilis.

The diagnosis of an abdominal aneurysm may not be considered and the diagnosis is impossible in some cases, as was demonstrated in a recent case, not included in this series, seen at a clinicopathologic conference. A male, aged 38, had for over a year complained of lower lumbar stiffness and slight pain. He was admitted to Charity Hospital a second time for this complaint. A diagnosis of lumbosacral arthritis was made and apparently confirmed by the Roentgen ray. Sudden death occurred. At necropsy was found an aneurysm about the size of a large orange just beneath the diaphragm where it could not have been palpated. It had ruptured into the left pleural cavity and had infiltrated the left leaf of the diaphragm and the retroperitoneal region of the left side. The vertebræ were deeply eroded (Fig. 2). If the Roentgen ray plate had included the upper lumbar vertebræ the diagnosis would have been made.

Several conditions must be considered in the differential diagnosis. Accentuation of normal pulsation of the abdominal aorta, as may be seen in advanced arteriosclerosis, or in the thin neurotic patient may suggest aneurysm. However, careful examination shows the absence of tumor and expansile pulsation.

Spinal arthritis may be simulated as indicated above, possibly due to involvement of the spinal roots. This diagnosis was made in several of the patients in this series. The presence of a pulsating tumor should point toward a diagnosis, and the Roentgen ray would give evidence for or against aneurysm with vertebral erosion or spinal arthritis.

Tumor of the liver, including malignancy, primary or metastatic, gumma, or abscess of the left lobe, of which we have recently seen 2, may at first glance simulate an aneurysm because of transmitted pulsation. However, the absence of expansile pulsation, the mobility of the tumor with respiration, and the usually palpable liver edge make the diagnosis without question.

Gastric carcinoma may present tumor with transmitted pulsation and may raise the question of abdominal aneurysm. If the tumor is movable with respiration, aneurysm is ruled out. A fixed carcinoma, due to extragastric extension, is diagnosed by lack of expansile pulsation, and by laboratory and roentgenologic studies of the stomach. It must be recalled that an aneurysm may cause a filling defect of the stomach due to extrinsic pressure.

In the past couple of years, we have seen pancreatic cysts simulate abdominal aneurysm. Both conditions present a tumor, and the cyst may present a transmitted pulsation which displaces the cyst laterally with each systole, simulating in a way an expansile pulsation. Further, in Roentgen ray studies made in the lateral position both may show displacement of the stomach anteriorly. We have seen both lesions with calcified walls. The diagnosis must rest on careful study of the pulsation; if erosion of vertebræ is present the diagnosis of aneurysm is made.

Differentiation of aneurysm from a mass of malignant retroperitoneal lymph glands may be still more difficult. Transmitted pulsation may be present, anterior displacement of the stomach with pressure defect may occur and erosion by invasion of the vertebræ may take place. In malignancy, however, the intervertebral disks are not spared, as they are in erosion due to aneurysm.

Renal tumor was considered in several cases of this series, and pyelography was resorted to in 1 case. Diagnosis is made on the basis of type of pulsation and the use of the Roentgen ray for spine and kidney studies.

Lastly, it must be recognized that, due to a thick laminated clot in the sac, no pulsation may be present, or at least be of such slight degree that expansibility cannot be determined. In such event the differentiation of aneurysm from some of the above conditions may be very difficult, if not impossible.

Prognosis and Death. Abdominal aneurysm is apparently a condition in which death may be expected within a short time after the onset of symptoms. In the series of 68 cases, death occurred in the hospital in 46 instances (66%). Death occurred within

1 month of hospitalization in 38 and in over one-half of these took place in less than 1 week after entering the hospital. Table 5 gives the time elapsed from admission to the hospital to death in the 46 cases. By a correlation of this table with Table 3 it can be readily seen that the majority of patients with abdominal aneurysm succumb to the process within 6 months from the time of onset of symptoms.

In 20 of the 46 patients dying in the hospital, death was described as being sudden, instantaneous or occurring in a few minutes. Death took place rather quickly, apparently a matter of several hours in 10 cases. Bleeding took place for 12 to 72 hours in 6 cases, as one might judge from notes as to coma, apparent loss of blood, with later necropsy. No note was made as to the rapidity of fatal issue in 9 cases. One patient obviously died of carcinoma of the esophagus, abdominal aneurysm being an incidental finding.

TABLE 5.—TIME FROM ADMISSION TO DEATH IN 46 CASES.

	No. cases.		No. cases.
1 to 3 days	17	4 to 8 wks.	2
3 to 7 "	10	2 to 3 mos.	4
1 to 2 wks.	3	5 to 6 "	1
2 to 4 "	9		

Death is due to rupture of the abdominal aneurysm in the majority of cases. As will be seen in the discussion of pathologic findings, this is most often retroperitoneal. The rapidity with which death ensues is related to the degree of rupture. Most often there is sudden exsanguination. However, we not infrequently see, in aneurysms of the thoracic aorta, that slow leakage of blood may occur with slower progress to death. Such circumstances were apparently at work in several cases of this series where death was not sudden, but still due to hemorrhage. Of the 38 cases coming to necropsy, 31 showed death due to hemorrhage. Nixon reported 152 deaths from rupture in his collected series of 233 cases. Among the 7 deaths from other causes, there were no sudden deaths, though 2 died in a few hours. Death by hematemesis occurred in 2 cases, 1 of which came to necropsy and showed rupture of the aneurysm into the stomach.

Pathologic Findings. Necropsy was performed in 38 cases. The sac in all of these arose from the abdominal aorta except in 3 in which the sac originated from the celiac axis. These were included in this study, however, for it would be impossible clinically to differentiate such aneurysms from those arising from the aorta itself.

In practically all cases the sac arose from the upper part of the abdominal aorta, that is, from the portion between the level of the renal artery and the diaphragm. The size of the sac varied from that of a hen's egg to that of the head of a child; commonly, the size was given as that of an orange or grapefruit. Practically all sacs contained laminated clots.

As noted above, death was due to rupture of the sac with hemorrhage in 31 of the 38 cases coming to necropsy. The hemorrhage was retroperitoneal in 15, about equally divided as to frequency on the right and the left side of the spine. Rupture was retroperitoneal in 1 case with subsequent rupture into the peritoneal cavity. In 4 cases, rupture was directly into the peritoneal cavity. Bleeding between the leaves of the diaphragm occurred in 2 cases. In 4 cases, in which necropsy was done by the coroner, it was merely stated that rupture had occurred, the site of bleeding not being given. It is of interest that in 3 cases rupture took place through the left leaf of the diaphragm into the left pleural cavity. In another case, the sac being adherent to the diaphragm, the blood infiltrated the diaphragm, posterior mediastinum, penetrated about the roots of both lungs and finally perforated into both pleural cavities. One of the aneurysms of the celiac axis ruptured into the stomach, with death by hematemesis.

Erosion of vertebræ was described in 13 of the necropsy protocols. Left-sided pleural effusion occurred in 4 cases. Other incidental pathologic findings were pulmonary tuberculosis in 1, aneurysm of the ascending arch in 1, carcinoma of the esophagus in 1 and cardiac hypertrophy in 4 cases. The anatomic evidences of syphilis were described under the section on Etiology.

Summary. Aneurysm of the abdominal aorta is a relatively uncommon lesion. From the records of Charity Hospital for the past 30 years there have been selected 68 such cases in which the diagnosis could not be questioned. This group is the largest which has ever been collected from any one institution.

The etiologic factors in the production of aneurysm of the abdominal aorta have been discussed, and the clinical features have been described.

Roentgenologic findings, of great importance in diagnosis, have been emphasized. Diagnosis of abdominal aortic aneurysm involves the consideration of a number of conditions and may be difficult or even impossible.

Prognosis in this lesion is poor, the majority of patients dying within 6 months from the onset of symptoms. Death is usually sudden and due to rupture of the aneurysm. The necropsy findings in 38 cases have been presented.

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ABDOMINAL PAIN OF VASCULAR ORIGIN.

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Vascular disease is not generally recognized as one of the causes of abdominal pain. Although so-called abdominal angina has been described for years, a lack of postmortem evidence has prevented its acceptance as a clinical fact. Thus, Sir William Osler and Sir Clifford Allbutt both favored the view that transient attacks of abdominal pain in arteriosclerotic individuals were manifestations of angina pectoris rather than of visceral arterial disease, and more recently Morley[1] has written that there is no evidence of vascular pain in the abdomen apart from that due to actual gangrene and peritonitis secondary to mesenteric vascular occlusion. Conner[2] has renewed interest in this subject by concluding on theoretical grounds that visceral arterial disease is analogous to coronary disease and plays a significant rôle in many hitherto undiagnosed cases of abdominal pain.

If, as Conner suggests, visceral arterial disease is analogous to coronary disease, the past histories of patients dying of mesenteric thrombosis ought to reveal evidence, in a certain percentage of cases, of chronic abdominal pain preceding the acute attack. With this point in mind, the histories of all patients dying of mesenteric vascular occlusion, confirmed by autopsy, in the Peter Bent Brigham Hospital have been reviewed. In 7 of 12 cases in which the occlusion was associated with arteriosclerosis, there was a story of chronic recurrent abdominal pain preceding the fatal attack by weeks, months or years. In all of these cases mesenteric arteriosclerosis appeared to be the most plausible cause of the abdominal pain but unfortunately in nearly every case varying degrees of coronary sclerosis rendered a convincing interpretation of the cause of the pain impossible. The following case, however, was selected as indisputable evidence of the occurrence of abdominal pain of vascular origin.

Case Report. E. W., a male laborer, aged 47, entered this hospital because of recurrent abdominal pain of 2 months' duration. At the onset of the present illness the pain was located about the umbilicus, did not radiate, and was definitely related to meals, occurring about 1½ hours after eating. The patient described it as a "hard lump in the stomach." He

thought that for a short time the taking of a daily enema and mild cathartics, and the avoidance of heavy meals had alleviated the pain, but the severity of the attacks gradually increased. On several occasions there was slight diarrhea but no nausea or vomiting. Studies at another clinic, including an Roentgen ray examination of the entire gastro-intestinal tract, were negative and the patient was discharged with a diagnosis of psychoneurosis. Four days later he was admitted to this hospital.

At the time of admission the pain was excruciating and constant. It was now associated with nausea and vomiting, but there was no jaundice, diarrhea or melena. On physical examination the patient was found to be well developed, but had obviously lost weight recently. Examination of the heart and lungs was not remarkable. There was very slight tenderness to deep palpation in the epigastrium, but there was no muscle spasm or distention. The leukocyte count was 20,000 per cmm. The erythrocyte count was 5,000,000 per cmm. The blood Wassermann test was negative, and the examination of the urine and cerebrospinal fluid was negative. Intravenous cholecystograms were interpreted as showing a poorly functioning gall bladder.

The patient appeared to be exaggerating his symptoms. Although mesenteric thrombosis was considered as a possibility, the long duration of symptoms appeared to make it unlikely and a tentative diagnosis of subacute cholecystitis was made. The patient expired suddenly on the ward, 3 days after admission to the hospital. Until a few hours before death no significant changes in the physical examination was noted.

Postmortem examination showed vascular occlusion involving the celiac axis, superior and inferior mesenteric arteries. Almost the entire small bowel and part of the large bowel were gangrenous. There were about 250 cc. of bloody fluid in the abdomen and there was a thin, fibrinopurulent exudate scattered throughout the peritoneum. The thrombotic process was an old and progressive one. The superior mesenteric artery had apparently been completely occluded at one time and had been recanalized. The occlusive process in the inferior mesenteric artery also showed evidence of recanalization. There was a fresh thrombus completely occluding the celiac axis artery. Microscopic examination confirmed the impression that the process had been going on for a considerable length of time. There was slight cardiac hypertrophy but no coronary sclerosis or valvular disease. The gall bladder, stomach, duodenum and kidneys showed no variation from the normal.

An evaluation of the clinical and pathologic evidence in this case leads one to the conclusion that a gradual occlusion of the mesenteric arterial system by progressive thrombosis was the cause of recurrent abdominal pain of 2 months' duration. Certain characteristics of this pain merit further consideration. First, although severe it was not sharply localized, did not radiate, and was not associated with muscular spasm or exquisite tenderness of the abdominal wall. Secondly, it was in the beginning, definitely related to the ingestion of food and only later became constant. On the basis of these characteristics the following hypothesis is submitted: Vascular pain in the abdomen is the result of an anoxemia of the intestinal wall and is a true visceral pain manifested through sensory neurones in the sympathetic nerves independently of the musculocutaneous pathways.

At the present time there are two major theories of the nervous mechanism for abdominal pain. One, the Mackenzie theory,[3] holds that true visceral pain does not occur but that impulses arising in

diseased viscera (in themselves insensitive to pain) pass by way of the sympathetic nerves, to the cord where they established an "irritable focus" and overflow into the specialized somatic pain tracts. Pain is thus referred to the peripheral somatic nerve endings in the area where the spinal overflow occurs. The other theory proposed by Morley[1] maintains that true visceral pain is conducted by sympathetic pathways directly to the brain independently of the somatic nerves. According to this conception, true visceral pain is not well localized and is not associated with rigidity or exquisite tenderness of the abdominal wall. Only when the parietal peritoneum is irritated and somatic nerve trunks are stimulated is the pain of diseased viscera well localized and associated with muscular rigidity ("peritoneo-muscular reflex"). Recently, interest has been aroused in the old conception that sensory neurones of somatic type exist, although in smaller numbers than is found in the skin, in the mesentery and elsewhere within the abdomen. Heinbecker, Bishop and O'Leary[4] have shown that sympathetic trunks contain myelinated fibers whose histologic structure and electrical conduction properties are identical with the peripheral sensory pain fibers, and Sheehan[5] has shown that the myelinated neurones of the Pacinian bodies in the mesentery travel with the sympathetic nerves. In view of these studies it is quite probable that the somatic nervous system is involved in the production of intraäbdominal pain.

There is considerable clinical evidence to support this concept of two independent pathways for abdominal pain. One, over sensory neurones that travel in the sympathetic trunks, causing pain which is not well localized, is non-radiating, and is not associated with muscle spasm or severe tenderness, and the other, over the cerebrospinal nerves that supply the parietal peritoneum, causing board-like rigidity and exquisite tenderness ("peritoneo-muscular reflex" of Morley). Thus the early pain of appendicitis is supposed to be a true visceral pain, while the late pain in the right lower quadrant, associated with marked tenderness and muscle spasm is due to direct irritation of the parietal peritoneum. Zollinger[6] has shown that distention of the gall bladder and common duct in conscious patients although causing considerable distress, does not reproduce the typical pain of biliary colic. He suggests that in true gall bladder colic there is an irritation of the parietal peritoneum, which accounts for the radiation of the pain to the back. The recent studies of Rivers[7] also lend support to Morley's hypothesis. From a group of cases in which direct examination of the tissues was made and an accurate history obtained he found that the pain of uncomplicated peptic ulcer is poorly localized, but if there is penetration of the ulcer it becomes sharply localized. Rivers concludes that the pain of uncomplicated ulcer is a visceral phenomenon manifested through the splanchnic nerves and that the localization of the pain in penetrating ulcer is due to stimulation of cerebrospinal nerves.

According to Ryle[8] distention of the hollow viscera is the usual cause of true visceral pain but the occurrence of severe pain without rigidity or exquisite tenderness in the case reported here is evidence that non-fatal or early mesenteric arterial thrombosis is capable of causing the same phenomenon. The exact mechanisms involved in the production of vascular pain are not definitely established. Sutton and Lueth[9] have produced evidence to show that the pain of angina pectoris is due to anoxemia of the cardiac musculature and Sir Thomas Lewis[10] believes that the pain of intermittent claudication is attributable to metabolites that accumulate in a functioning muscle inadequately supplied with blood. The intermittent character of the pain and its definite relation to the ingestion of food, in the case reported above, suggests that a similar factor may be the cause of vascular pain in the abdomen. The partially occluded vessels, although adequate for viability of the bowel, were unable to meet the increased demand for blood necessary for function and a relative ischemia of the bowel occurred exactly as in the arteriosclerotic leg that is overexercised. Later on as the thrombosis progressed the circulation became inadequate even for the requirements of the bowel at rest. This was manifested clinically by persistence of the pain. Finally gangrene resulted in peritonitis and death.

The clinical importance of vascular pain in the abdomen lies in the fact that it may be the precursor of fatal mesenteric vascular occlusion and a proper appreciation of its characteristics is of great importance in the early recognition of this highly fatal condition. As seen in the reported case, the pain that occurs early in this condition differs from simple vascular pain only in its constancy. It also has the characteristics of true visceral pain as it is not associated with muscular spasm or exquisite tenderness until peritonitis has been established. In a previous communication[11] this contrast between the severity and persistence of the pain and the paucity of physical findings was pointed out as one of the most significant diagnostic features of mesenteric vascular occlusion. Recently, we have had an opportunity to confirm these impressions in the case of a young man with rheumatic heart disease who had an embolic occlusion of the superior mesenteric artery. There was severe pain with only moderate tenderness and no rigidity. At operation a few hours after the onset of the pain the bowel was found to be contracted, grayish in color, but not yet gangrenous and there was no evidence of peritonitis. No line of demarction could be made out so closure without resection was done. During the next 48 hours there was no definite change in the physical findings but the patient appeared definitely worse and at a second exploration the entire small bowel was found to be infarcted but not yet gangrenous and peritonitis had not yet developed. However, the operator felt that the lesion was too extensive to permit resection and the abdomen was closed without drainage. Although masked by liberal doses of morphin, definite signs of peritonitis, characterized by distention

and muscular spasm later developed and autopsy revealed gangrenous bowel and peritonitis. The superior mesenteric artery had been occluded at its base by an embolus. This lack of spasm and exquisite tenderness in the early stages of mesenteric vascular occlusion is in striking contrast to the boardlike rigidity of perforated ulcer or acute pancreatitis and constitutes a valuable diagnostic feature of the condition.

Summary. Evidence is presented to show that vascular disease of the mesentery can cause abdominal pain in the absence of gangrene or peritoneal irritation. It is suggested that pain so caused is the result of an anoxemia of the intestinal musculature, and is a true visceral pain conducted by sensory neurones in the sympathetic nerves independently of the musculocutaneous pathways. The importance of recognizing the characteristics of this type of pain in the early diagnosis of mesenteric vascular occlusion (arterial) is emphasized.

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VASCULAR CHANGES IN INTERMITTENT CLAUDICATION.

With a Note on the Value of Arteriography in This Symptom Complex.

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Although intermittent claudication has been recognized for many years as a possible concomitant of peripheral vascular disease, many phases of the condition are still obscure and little under-

stood. For one thing, it is a very inconstant phenomenon, and its presence seems entirely unrelated to the type of vascular disease with which it is associated, or to its degree. It frequently is evident in patients whose disease process never passes beyond the initial stage, and it is just as frequently absent in others who exhibit terminal gangrene. Again, the origin of the pain of intermittent claudication has never been satisfactorily explained, and even the most logical theory, as we shall point out shortly, is still largely hypothetical. Finally, so far as we are able to ascertain, the pathologic changes of intermittent claudication have never been described *in vivo*, though they have been thoroughly studied in the laboratory and at the postmortem table. With the second and third of these considerations, and more particularly with the third, this present communication is concerned.

The various theories advanced to explain the pain of intermittent claudication have been excellently summarized by Lewis, Pickering and Rothschild,[1] in a valuable communication in which are set forth also the results of their own experiments in this field. Charcot,[2] they point out, believed that the basis of the pain is a muscular cramp, comparable to the so-called "cadaveric rigidity," which is the result of a deficient blood supply to the parts. Marinesco,[2] arguing along the same lines, advanced the idea that the cramp occurs because the blood supply to the muscles is inadequate during exercise, although it is entirely adequate during rest. Goldflam and Erb,[2] although they accepted the theory of muscular cramp, admitted the possibility of other extramuscular structures, such as the arteries or even the skin, being the seat of the pain.

But muscular cramp, as Lewis and his co-authors point out, and as every careful observer knows, although it may be associated with intermittent claudication, is by no means a constant concomitant and is by no means essential to its production. We would suggest, as an interpolation of our own, that perhaps the theory of muscular cramp arose originally merely because the usual patient, hampered by the difficulty of translating his discomfort into words, used the term "cramp" to describe his pain. Other theories have arisen on no sounder foundation.

Kissin's[2] theory, that the cause of exercise pain is an anoxemia produced in the muscles from an obstruction of the arterial blood supply, is disproved, Lewis and his associates point out, by their own observations. They were able to show that obstruction of the vessels before exercise, even for 10-minute periods, does not initiate the pain, and that continuation of the obstruction after the exercise pain has reached its acme does not aggravate it. Furthermore, they showed by repeated tests in the same individual that the pain does not occur at all if the exercise is discontinued just before the pain is anticipated, though at this time the "oxygen debt" would supposedly be at its height.

The theory of arterial spasm was first suggested by Erb,[2] who did not believe that mechanical narrowing of the bloodvessels was sufficient to explain the whole picture, and it has been championed since by other observers, notably by Zak.[2] But Lewis and his co-authors, while granting the truth of Zak's observations, are unwilling to accept them in their universal application. Zak's theory is based on the following experiment: After the circulation was shut off, the patient was required to open and close his hand energetically until, usually at the end of 30 such movements, the fingers became white and cool and exercise pain appeared. The circulation was then released. In all of Zak's observations the blood did not return to the fingers for several seconds, sometimes as long as 10 seconds, the delay, in his opinion, being evidence of vascular contraction. Lewis[3] grants that the contraction is present, but is unwilling to grant that it is due to spasm; he explains it by the fact that the fingers have become cold during the exercise, and that cold always contracts the digital arteries. When he and his associates made the same observations with the fingers warmed, they found that the pain still occurred, but that there was rarely any delay in the return of the circulation to the hand, just as there was no appreciable delay in its return to the control hand if it were similarly warmed but not exercised. Lewis explains the few cases in which, after the release of the obstruction, there was a delay in the return of the circulation to the exercised hand, by the diversion of the blood to the greatly dilated vessels of the muscles of the forearm.

The theory which Lewis and his co-workers have advanced to explain the pain of intermittent claudication is based on an elaborate set of experiments dealing with the production of ischemic pain by obstruction of the arterial supply. On the basis of these experiments they conclude that the pain is caused by a product of muscular metabolism, which they term factor P. The background, so to speak, is an inadequate blood supply to the muscles of the parts, the inadequacy being evident only during exercise. When successive muscular contractions occur, the state of the muscle undergoes a progressive alteration, and as this alteration takes place, its product, the hypothetical factor P, is given off and collects in the extramuscular tissue spaces. Factor P, which is a physicochemical product with a cumulative action, is given off during exercise, they believe, even when the blood supply to the muscle is adequate, but under those circumstances it does not rise to the pain level in the tissue spaces. In other words, although obstruction to the blood supply is the essential basis of the pain, the pain stimulus itself, the hypothetical factor P, is a product given off by the muscle fibers. The theory is ingenious, but obviously, until factor P has been isolated, it must remain only a theory.

Our present communication is based on the study by arteriog-

raphy of 15 carefully selected cases of intermittent claudication which have been observed during the last 3 years. Fourteen patients were male and 1 female, 12 were white and 3 colored, but this distribution, in so small a number of observations, probably has no particular significance. The age range was from 23 to 77 years; 4 patients were between 30 and 40, 3 between 40 and 50, 5 between 50 and 60 and 3 over 60. The duration of symptoms varied from 2 months to 4 years.

All of these patients had perfectly typical histories, which, in a composite form, were about as follows: The first symptom noted was a sense of fatigue after walking, sometimes in one leg, more usually in both, and always eventually in both. By slow degrees this sense of fatigue passed over into actual pain, which, by equally slow degrees, increased in severity; it was always confined to the calf muscles. At first it was noted only after a long walk, then it began to occur after shorter and shorter walks, and finally it occurred, with great severity, after a walk of only a short distance, sometimes only a few hundred feet. At first it was relieved by rest, but longer and longer intervals of rest became necessary to relieve pain which occurred after shorter and shorter walks, and finally the patient was for all practical purposes physically incapacitated. The pain was usually described as a cramping or drawing sensation in the muscles of the calf, and it naturally varied in the individual patient in its duration and severity, and in the amount of exercise necessary to produce it.

In 12 cases the etiologic basis was definitely arteriosclerotic, and the patients in this group, in addition to intermittent claudication, exhibited other evidences of arteriosclerotic disease, chiefly beading of the arteries, absence of the dorsalis pedis pulse, pallor and coldness of the extremities, exaggeration of the pain on exposure to cold, and night pain of varying degrees of severity. In the remaining 3 cases, which will be discussed later in detail, the etiologic basis could not be definitely determined. In all 15 cases syphilis was not a factor, and Buerger's disease was also eliminated, in order that the vasospastic and inflammatory phenomena characteristic of it should not confuse the picture.

These 15 cases were studied by means of arteriography of the regional blood supply with stabilized thorium dioxid (Thorotrast Heyden). This agent, as we have pointed out in other communications,[4,5,6] is an opaque substance admirably adapted for visualization of the vascular tree. It has no perceptible effect on the diseased vessels, it is non-toxic in the dosage necessary for the purpose, and in an experience of almost 3 years, in over 300 cases, we have noted no deleterious effects from its use.

In all instances the pain of which the patients in this series complained was confined to the muscles of the calf, and for purposes of comparison it was, therefore, necessary to establish the

FIG. 1.—Normal vascular supply of the popliteal region in a white male, aged 45 years.

FIG. 2.—Complete obliteration of the popliteal artery, with narrowing of the tibial vessels, in a case of intermittent claudication. Note the large collateral vessels.

FIG. 3.—Marked narrowing of the femoral, popliteal and tibial vessels in a case of intermittent claudication. Note the reduction in the number and size of the muscular branches.

FIG. 4.—Intermittent claudication of undetermined origin. Note the peculiar dilatation and clubbing of the muscular branches, the marked narrowing of the popliteal artery, and the numerous small collateral vessels.

FIG. 5.—Blood supply of the popliteal region during rest in a case of intermittent claudication. Note the narrowing of the popliteal artery and the obstruction of the anterior tibial artery.

FIG. 6.—Blood supply of the popliteal region during exercise pain in the case of intermittent claudication shown in Fig. 5. Note the dilatation of the larger vessels and the presence of numerous fine vessels not visualized during life.

FIG. 7.—Arteriography 14 months later, after treatment, in the case of intermittent claudication shown in Fig. 2. Note the slight increase in the size of the large arteries and the more marked increase in the number of small branches supplying the soft parts.

normal picture of the regional blood supply. Repeated observations have established the following criteria, which can be noted in Fig. 1.

1. The femoral, popliteal and tibial arteries are smooth and regular in their course, without narrowing of the channel at any point by plaques or other obstructions.

2. The large muscular branches are long and evenly distributed.

3. The small muscular branches are numerous and are given off at regular intervals from the larger branches. They terminate in fine twigs, which, in turn, supply even finer twigs to all parts of the soft tissue.

On the basis of the hallmarks of the normal vascular supply, namely, smoothness of contour, regularity of pattern, and adequacy of size and distribution, we studied the arteriographs of these patients with intermittent claudication. In addition, we noted particularly the size and distribution of the collateral circulation. Our experience with arteriography in various types of peripheral vascular disease has made us aware of the fact that the collateral circulation, however efficient it may be, cannot possibly be as efficient as the normal circulation because it practically never reaches all of the smaller muscular fibers. It should be stated that all of the arteriographs, except when otherwise specified, were taken during the rest period.

The arteriographs fall into 3 distinct groups. In the first group (6 cases) the etiologic basis was arteriosclerosis, and the most outstanding change was obliteration of the large arteries. In 3 cases the obliteration involved only the popliteal artery (Fig. 2), in 2 it involved the tibial vessels just below their point of origin and in the remaining case it involved the popliteal and lower femoral arteries. In the cases in which the tibial vessels were obliterated the popliteal vessels were markedly narrowed, just as in those cases in which the popliteal vessels were obliterated, the tibial vessels were markedly narrowed. In all 6 cases in this group there was a diminution in the number of the large muscular branches, and their distribution was uneven and clearly inadequate. The 4 cases in which the popliteal artery was completely obliterated showed many new collateral vessels, which were, however, inadequate in their distribution.

In the second group (6 cases) the etiologic basis was again arteriosclerosis. In these cases the large arteries were not obliterated, but the lumen was markedly narrowed (Fig. 3), especially in 3 cases in which the encroachment of plaques caused definite areas of constriction. In this group also there was a marked diminution in the size of the muscular branches and in the number of the finer muscular terminals. In the 3 cases in which plaques were not present, the main pathologic change was confined to the large and small muscular branches, which were so reduced, both in number

and size, that in only a few areas did the vascular pattern approach the normal; in other areas there were few visible branches and sometimes none at all. In all 6 cases in this group the new collateral blood supply was frankly inadequate.

The most important vascular changes in these first two groups, then, included in one group obliteration of the large arterial trunks and in the other more or less diminution in the size of the lumen of the arterial trunks, and marked diminution in both the size and number of the large and small muscular branches. The collateral blood supply, although apparently adequate in the number and size of its branches, was practically always inadequate in distribution.

The last group includes the 3 patients in whom no etiologic basis for the intermittent claudication could be discovered. All 3 of them gave a history of some prolonged febrile disturbance of unknown origin in early adult life; in 2 cases this illness was associated with pain in the extremities, and can be assumed to have initiated the vascular disturbance.

The first patient, who showed the least marked variation from the normal on radiographic study, had, curiously, the most acute symptoms. He was a negro male, aged 23 years, who came into the hospital complaining that he could walk only a few feet without pain. Even at rest he had pain, which was increased by palpation, in the calf muscles and the toes. The dorsalis pedis pulse was palpable bilaterally, and there were no gross changes in the extremities. There was no febrile reaction. Arteriographic study showed a peculiar clubbing and dilatation of the muscular branches, which terminated very abruptly. No change was evident in the main arteries.

The second patient was a white male, aged 40 years, who gave a typical history of bilateral intermittent claudication after walking two blocks. The dorsalis pedis pulse could not be made out. Arteriography showed the same peculiar configuration of the muscular branches described in the first case, which was associated with a narrowing of the popliteal and tibial arteries (Fig. 4).

The third patient, a white male, aged 46 years, complained of the same symptoms and exhibited the same type of vascular damage already described, except that in this case the process included the popliteal artery, which was completely obliterated.

We have, then, a group of 3 successively older patients, in each of whom successively more serious vascular changes are exhibited. All the evidence goes to prove that the process, whatever it may be, begins in the muscular branches, which are typically short and clubbed, and finally progresses to the large arteries, which eventually are completely obliterated. We might add that, although we have not secured biopsy specimens from any of these patients, such an investigation should certainly be undertaken in an endeavor further to elucidate this curious pathologic picture.

Lewis' experiments, as we have already mentioned, eliminate arterial spasm as the cause of the pain of intermittent claudication; indeed, he was able to show that immediately after the release of the vascular obstruction, and while ischemic pain is still felt, the blood supply to the parts is increased, sometimes 20 times over the resting circulation. We have been able to corroborate his observations by the following tests upon a patient with intermittent claudication:

A white male, aged 46 years, told a typical story of intermittent claudication produced by walking two blocks. After a prolonged rest period he was lifted from a rolling chair to the Roentgen ray table. Arteriography at this time (Fig. 5) showed a marked narrowing of the popliteal artery, with obstruction of the anterior tibial artery at several points, and a marked diminution in the size of the muscular branches. There was evidence of a newly formed collateral circulation. Two days later this patient was made to walk until the pain in his calf muscles had completely incapacitated him; after he was allowed to rest, it was fully 5 minutes before the pain began to disappear, and it persisted in a milder form for 5 or 6 minutes longer. Following another long period of rest, he was again made to walk until he was incapacitated; then, with as little delay as possible, he was lifted to the Roentgen ray table and another arteriogram was taken. The whole procedure consumed not more than $1\frac{1}{2}$ minutes, and the intense pain persisted, as at the first test, for more than 5 minutes. This arteriogram (Fig. 6) showed an increase in the size of the arterial lumen, some enlargement of the muscular branches, and the visualization of numerous fine branches not seen in the first picture.

This observation, therefore, bears out Lewis' contention that the blood supply to the extremity is increased rather than decreased at the height of the pain, and furnishes at least indirect support to his theory that some physicochemical change in the nutrition of the muscles is the cause of the pain. The theory is further supported by the fact that in all 15 of our cases some distinct change can be made out in the nutrition of the muscles. In some instances the change was in the muscular branches alone, in others the principal change was in the large arteries and the muscular branches were only secondarily affected, but always the arteriographic evidence supported the theory that impairment of the muscular nutrition was the basis of the pain.

Some of the patients in this series we have been able to study over many months, and successive arteriograms have proved very interesting. One of these cases might be mentioned in detail, for it proves very clearly that intermittent claudication is really a blessing in disguise, in that it forces patients, because of their pain, to seek medical advice far earlier than they would otherwise. The intensity of the pain, furthermore, and the resulting incapacitation make them unusually coöperative.

A white male, aged 72 years, entered the hospital 14 months ago complaining of pain in both calves after walking even half a block. Four months before admission he had begun to have a drawing sensation in the calf muscles of both legs after walking any considerable distance. This discomfort gradually merged into pain, and when he was first observed he could walk only a few hundred feet without stopping to rest. He exhibited the typical signs of arteriosclerosis, including a bilateral absence of the dorsalis pedis pulse, he had severe night pains and all his symptoms were aggravated by exposure.

Arteriography at this time (Fig. 2) showed a complete obliteration of the popliteal artery at its middle portion, and a marked narrowing of the femoral artery, which was constricted at several points by the encroachment of large plaques upon its lumen. The blood supply of the calf muscles was from a large branch from the lower third of the femoral artery, which passed below the knee and terminated at the junction of the upper and middle third of the leg, and from 3 large branches of the popliteal artery, which arose just above the point at which it was obliterated and which descended well down into the leg. The number of large and small muscular branches was apparently adequate, but their distribution was not, and it was apparent that many areas had a poor blood supply or none at all.

This patient was treated intensively with diathermy, contrast baths, hot baths twice a day, and vascular exercises so graded that they stopped just before pain was precipitated. At the end of 3 months, although he still noted a sense of fatigue in his calf muscles, he was able to walk several blocks in comparative comfort. The arteriogram at this time practically duplicated the first picture. Now, at the end of 14 months, he can walk 25 blocks without pain. He begins to feel fatigued at the end of 12 or 14 blocks, but he can walk, more slowly, almost twice as far. His night pain, although less troublesome, still persists. Arteriography at this time (Fig. 7) still shows little change from the original picture; there is a slight widening of the tibial vessels, some enlargement of the large branches of the popliteal artery, and perhaps a slight improvement in the collateral circulation, particularly in the very fine branches.

Quite evidently the improvement in the blood supply is not enough to explain this patient's clinical improvement. Our interpretation of the change in his symptoms is that the regional blood supply, at least for several hours each day, is so much increased by heat and exercise that the hypothetical factor P of Lewis does not reach the pain level. It may be, too, that the temporary improvement in the nutrition of the parts actually alters the physicochemical changes which occur as the result of exercise. Whatever the explanation, there is no doubt that the patient has improved. He has been tided over the crisis that, without treatment, might have terminated in irremediable disease, and the chances are that even

if no further improvement occurs, there will be no further extension of his disease.

One other point should be noted, that arteriography is a valuable means of making a differential diagnosis in obscure cases of pain in the extremities in which the vascular lesions are not evident grossly. Such cases are frequently diagnosed as arthritis, neuritis and other extravascular conditions, and the golden opportunity is lost of arresting the disease as it was arrested in the patient whose history we have just outlined.

Summary. 1. The theories of the origin of pain in intermittent claudication are briefly reviewed.

2. An arteriographic study of 15 carefully selected cases of intermittent claudication is reported.

3. Attention is called to the fact that in 3 cases of undetermined etiology the radiographic evidence shows an entirely different type of lesion from that noted in the other 12 cases, in which the etiology was arteriosclerotic.

4. Arteriographic evidence is adduced to support the contention that the pain in intermittent claudication is not due to arterial spasm.

5. An illustrative case is cited to show that the improvement which follows heat, exercise and similar measures in intermittent claudication is not due to any notable change in the vascular supply but presumably to the temporarily increased nutrition of the parts which is achieved by this form of therapy.

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BOOK REVIEWS AND NOTICES.

CLINICAL MISCELLANY, *Volume 2, 1935. The Mary Imogene Bassett Hospital, Cooperstown, N. Y.* By 9 Contributors. Pp. 218; illustrated. Baltimore: Charles C Thomas, 1935. Price, $3.00.

THIS volume comprises 20 papers by 9 contributors from the Bassett Hospital, the majority, case reports. In general the cases are well selected and the study that each case has received reflects much credit on the Hospital as well as on the individual authors. From the standpoint of the general reader, Volume II represents a decided advance over its predecessor in that more of the papers deal with series of cases instead of with single occurrences of very rare conditions. The new volume is further improved by a number of excellent illustrations and by frequent brief discussions of the literature which serve to orient the reader if he is unfamiliar with the field. Of particular interest were the epidemiological study of poliomyelitis in a rural community by F. F. Harrison and M. F. Murray, the paper on post-vaccinal polyneuritis by F. F. Harrison, a study of Bacteremia based on over 1200 blood cultures by G. M. Mackenzie and R. M. Pike, and the report of a case of fatal hemorrhage complicating scarlet fever by M. F. Murray.

J. R.

A MANUAL OF THE COMMON CONTAGIOUS DISEASES. By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 437; 53 illustrations and 3 plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $4.00.

PRACTITIONERS and students will welcome the new edition, enlarged and thoroughly revised, of this practical, well-written, handy little volume that testifies to the author's clinical and teaching experience. R. K.

GRUNDZÜGE DER PRAKTISCHEN SEELENHEILKUNDE. By DR. MED. FRITZ KÜNKEL, Berlin. Pp. 168. Stuttgart: Hippokrates Verlag. Price, Rm. 6.75, paper binding; Rm. 8, linen binding.

A PRACTICAL text for the general practitioner. The author points out that the increasing complexity of psychiatry has been increasingly confusing to the general practitioner, yet he is the one who is particularly in need of knowledge of the subject, since in his daily practice he is the first to encounter the numerous psychiatric problems in their inception. Just as books are written on "minor surgery" to meet the needs of the general practitioner, so in this instance the author places his emphasis largely on "minor psychiatry" (although some of the illustrative case material is decidedly "major"). The book will make interesting and profitable reading for all clinicians with a knowledge of German. R. K.

YOU MUST EAT MEAT. Fancies, Foibles and Facts About Meat. By MAX ERNEST JUTTE, M.D., Formerly Lecturer on Stomach and Intestinal Diseases, New York Policlinic Medical School, etc. Pp. 164; illustrated. New York: G. P. Putnam's Sons, 1936. Price, $2.00.

A TIMELY book presenting in readable fashion the case for a well-balanced diet. It is an authoritative criticism of the present tendency toward over-indulgence in "rabbit food." W. J.

LE SANG DES HYPERTENDUS. By GEORGES CARRIÈRE, Professor of Clinical Medicine, and CLAUDE HURIEZ, Chief of the Medical Clinic at the Faculty of Medicine of the University of Lille. Pp. 386; 53 tables. Paris: G. Doin et Cie, 1936. Price, 50 fr.

THIS work comprises a study of the physical and chemical characteristics of the blood in the presence of arterial hypertension. It is based upon the published reports of the authors and their co-workers of some 2000 determinations made in a series of 105 selected cases.

Hypertension is classified according to whether it occurs as an isolated phenomenon, is complicated by other disease or is simply associated with other disease. Although the blood pattern is somewhat different in these 3 groups, it seemed to the authors of greatest interest that there was a consistent alteration of the lipoids and proteins, together with an increase in osmotic pressure. These changes they regard as intermediary between the hypertension and a widespread metabolic disorder, essentially endocrine in background and involving especially the adrenals, thyroid and liver.

The book contains excellent tables presenting all data made in the course of the authors' study. It includes also a fair review of current opinion on the subject, together with a bibliography of 800 references, predominantly French. It is, in short, a complete expression of the authors' views on the alterations of the blood in hypertension and may therefore be recommended as being of interest to investigators in this field. L. L.

LOBAR PNEUMONIA AND SERUM THERAPY. With Special Reference to the Massachusetts Pneumonia Study. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 91; 10 figures and 1 plate. New York: The Commonwealth Fund, 1936. Price, $1.00.

THIS handbook deals with lobar pneumonia and its treatment with serum. It discusses the Neufeld technique for the rapid determination of the pneumococcus type, the technique and results of serum administration, and serum reactions and their prevention.

This brief work, written in the light of the Massachusetts pneumonia study, should prove decidedly helpful to practitioners who are interested in lowering their mortality by the use of serum. J. A.

ATLAS OF PATHOLOGICAL ANATOMY, *Volume 2*. Compiled by E. K. MARTIN, M.S., F.R.C.S. Issued under the Direction of the Editorial Committee of the British Journal of Surgery. Pp. 475; 268 illustrations (168 in colors). Baltimore: William Wood & Co., 1935. Price, $15.00.

THIS second volume continues the method of presenting gross pathology and the high standard of the first. All of the illustrations are life-like yet accurate, and considerably more than half in well reproduced colors. This last item in itself would make the price prohibitive if the book had been printed in this country, rather than in England. The 55 sections of this volume cover lesions of the joints, fibrocystic disease of bone, the thyroid the gastro-intestinal tract, the bladder and male genital tract, and a few miscellaneous conditions. Most of the illustrations are full page, with a description and points from the clinical history on the opposite page. As an adjunct to the study of actual lesions in the museum, or better at the autopsy table when possible, this book should be valuable to graduate and undergraduate students as well as to practitioners who attempt to keep their knowledge of pathology fresh and useful. E. K.

AMERICAN CHAMBER OF HORRORS. The Truth About Food and Drugs. By RUTH DEFOREST LAMB. Pp. 418; illustrated. New York: Farrar & Rhinehart, 1936. Price, $2.50.

"THE book points out the abuses in the cosmetic industry that flourish because the Federal Government has no control over beauty preparations, however harmful they may be; reveals the jokers in the present law that prevent the carrying out of its original purpose as respects both food and drugs; shows how and why the Government is powerless to do anything about abuses which have grown up since the Wiley law was enacted; shows the rackets that flourish because there is no control of advertising; tells the inside story of the Food and Drug Administration's fight to protect consumers against poisonous spray residue—the first time it has ever been told; takes the lid off the butter industry and exposes incredible conditions, showing how and why they exist and how they could be corrected; tells how the farmers are swindled with veterinary frauds; gives glimpses behind the scenes in an exciting but unpublicized Government agency that the public really knows very little about; indirectly shows the kind of men in charge of enforcement; though it is not official, could not have been written by anyone outside the Government." (From the Publishers' jacket.)

GASTRITIS AND ITS CONSEQUENCES. By KNUD FABER, M.D., LL.D., ENG., F.R.C.P., ENG., HON., Professor of Internal Medicine in the University of Copenhagen. Pp. 119; 48 illustrations. New York: Oxford University Press, 1935. Price, $3.00.

"THE wheel is come full circle." A generation ago, "gastritis" was a diagnosis frequently made. But with the introduction of Roentgen rays and increasing surgical exploration of the stomach, "gastritis" gave way to organic (ulcer) or functional (gastric neurosis) diagnoses. But once again, newer knowledge of disease (*e. e.*, pernicious anemia) and newer methods of study (*e. g.*, gastroscopy) have reclaimed "gastritis" from its near-oblivion and placed it in a higher and more significant place than ever. The chapter headings tell the story: Acute and Chronic Gastritis (Normal Appearance of the Stomach); Gastritis and Hyperacidity (Pyloric Gastritis, Gastritis as the Cause of Ulcer); Gastritis and Anacidity (Gastritis and Pernicious Anemia). The author is eminently qualified to present the subject, for his researches have played a most important rôle in its development. All clinicians will welcome this little volume. R. K.

DELAFIELD AND PRUDDEN'S TEXT-BOOK OF PATHOLOGY. Revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Pp. 1046; 839 illustrations and 22 full-page plates, many in color. Sixteenth edition. Baltimore: William Wood & Co., 1936. Price, $10.00.

THIS sixteenth edition, appearing 51 years after the first, is put forth as a jubilee edition. As its reviser points out, it was the first important American textbook of pathology after Gross' work (1839), which was practically the first American book on the subject. What a chance to follow the development of pathology during its most important period! But the editor claims to have resisted the pressure to make the new editions more modern on the specious ground that people have the same lesions as earlier, though the names may have changed. Such a policy, to be sure, makes the work more easily available "as a reference work by those long past their student days," who will be more at home with the parenchymatous

and vascular types of chronic nephritis, for instance, than with the later classifications now generally in use. Fortunately, however, the policy has not always been carried out. The section on tumors, for instance—almost 100 pages—makes the best modern presentation of the subject that can be found in a one volume textbook—a result not to be wondered at in view of the editor's eminence in this field. The chapters on the Nervous System, the Muscles, Bones and Joints show extensive changes, and the rich bibliography shows many references of recent date. E. K.

DIFFERENTIALDIAGNOSE IN DER INNEREN MEDIZIN. By PROF. DR. MED. O. NAEGELI, Direktor der medizinischen Universitätsklinik, Zürich. Pp. 216; 55 illustrations, some in colors. Leipzig: Georg Thieme, 1936. Price, M. 9.60.

EMPHASIZING general biological concepts rather than "minor signs which seldom can give anything important to differential diagnosis," this book aims to show the practitioner how to get further help—usually in laboratory methods. Especially in disorders of blood and spleen, that occupy most of this section, does the author feel that this applies. Disease pictures are not given and, while the important differential points are valuable for reference, they seem too much condensed to permit the work to serve as more than a useful adjunct to more complete presentation of the diseases covered. E. K.

AUS MEINEN KRANKENBLÄTTERN. Von der Arbeit eines Landarztes. By DR. AUGUST HEISLER, Sanatorium Luisenruhe und Kinderweide Königsfeld im Schwarzwald. Pp. 68. München: Verlag der Arztlichen Rundschau, Otto Gmelin, 1936. Price, Paper, Rm. 1.58; Bound, Rm. 2.25.

THIS is pamphlet No. 47 of a collection of diagnostic and therapeutic dissertations for the practitioner. It consists of five addresses by the author on topics ranging from case reports of the results of leeching to the dedication of a village water main. R. K.

NEW BOOKS.

Abortion. Spontaneous and Induced. Medical and Social Aspects. By FREDERICK J. TAUSSIG, M.D., F.A.C.S., Professor of Clinical Obstetrics and Clinical Gynecology, Washington University School of Medicine, St. Louis. (This volume is one of a series dealing with medical aspects of human fertility sponsored by The National Committee on Maternal Health, Inc.) Pp. 536; 146 illustrations and 27 tables. St. Louis: The C. V. Mosby Company, 1936. Price, $7.50.

The Harvey Lectures, Series XXX. Delivered under the Auspices of The Harvey Society of New York, 1934–1935. Under the patronage of the New York Academy of Medicine. By DRS. WM. BOSWORTH CASTLE, WILLIAM CUMMING ROSE, WILBUR A. SAWYER, ALFRED N. RICHARDS, E. C. DODDS, G. V. ANREP, FRANCIS G. BLAKE and JOHN H. NORTHROP. Pp. 270; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, $4.00.

The Adrenals. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics, and formerly Associate Professor of Physiology in the Medical School of The Johns Hopkins University. Pp. 410; 17 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, $5.00.

The Common Cold and Influenza. And Their Relationship to Other Infections in Man and Animals. By J. E. R. McDonagh, F.R.C.S. Pp. 152. London: William Heinemann, Ltd., 1936. Price, 12s. 6 d.

The 1935 Year Book of General Surgery. Edited by Evarts A. Graham, A.B., M.D., Professor of Surgery, Washington University School of Medicine; Surgeon-in-Chief of the Barnes Hospital, and of the Children's Hospital, St. Louis. Pp. 838; 206 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, $3.00.

This volume, one of ten that has been appearing annually for 35 years, covers the advances in the field of surgery in the past 2 years. Similar volumes appear from the same publishing house on General Medicine; General Surgery; Eye, Ear, Nose and Throat; Pediatrics; Obstetrics and Gynecology; General Therapeutics; Urology; Neurology, Psychiatry and Endocrinology; Dermatology and Syphilology, and Radiology. While most of the matter is classified according to regions of the body, there are also subdivisions on Anesthesia, Asepsis, Operative Technique, Wound Healing and Pathologic Interventions, Tetanus, Malignant Tumors, and Orthopedic Surgery. The book contains a wealth of information, some of it of more statistical than intrinsic value. The chief increases are found in the fields of peripheral vascular and thoracic surgery. American literature does not predominate.

Allergy of the Nose and Parnasal Sinuses. A Monograph on the Subject of Allergy as Related to Otolaryngology. By French K. Hansel, M.D., M.S., Assistant Professor of Clinical Otolaryngology, Washington University School of Medicine; Fellow of the Association for the Study of Allergy, etc. Pp. 820; 58 illustrations, 4 charts and 58 tables. St. Louis: The C. V. Mosby Company, 1936. Price, $10.00.

Lecciones de Patología Médica. Tome 2. By Dr. C. Jimenez Diaz. Tomadas taquigráficamente por el Dr. J. De Paz Montalvo. Pp. 1403; 297 illustrations. Barcelona: Editorial Cientifico Medica, 1936. Price not given.

This second volume, the first not having been received, devotes 156 lectures to the pathologic anatomy and physiology of the kidney, the nervous system, the lungs, the circulatory, and digestive tracts. The first two occupy three-fourths of the total space.

Interpretation of Laboratory Findings. By Raymond H. Goodale, M.D., Pathologist, City Hospital, Worcester, Mass.; Visiting Pathologist, Belmont and Fairlawn Hospitals, Worcester, etc. Pp. 170. Philadelphia: F. A. Davis Company, 1936. Price, $2.25.

Biological Effects of Radiation. Mechanism and Measurement of Radiation Applications in Biology, Photochemical Reactions, Effects of Radiant Energy on Organisms and Organic Products. Vols. 1 and 2. Prepared under the Auspices of the Committee on Radiation, Division of Biology and Agriculture, National Research Council, Washington. Edited by Benjamin M. Duggar, Professor of Plant Physiology and Applied Botany, University of Wisconsin, with the coöperation of Janet Howell Clark, Kenneth S. Cole, Farrington Daniels, Gioacchino Failla, Charles Packard and Henry W. Popp. Pp. 1342; illustrated. New York: McGraw-Hill Book Company, Inc., 1936. Price, $12.00.

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NEW EDITIONS.

The First Decade, 1926–1936. The University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital. Pp. 208; illustrated. Second edition. Rochester, N. Y.: By the University. Price not given.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PERNICIOUS ANEMIA.

Etiology.—Although the stomach in pernicious anemia has held the interest and attention of many observers for over 50 years, especially since Henry and Osler[1] described in this journal the morbid changes present, it was not until 1929, when Castle[2] published, also in this journal, his important observations, that an understanding of the rôle of the stomach began to unfold itself. These studies and subsequent contributions by Castle and a legion of investigators stimulated by his work, have not only established the pathogenesis of pernicious anemia upon a solid foundation but have also brought to light an understanding of the etiology and therapy of certain related macrocytic anemias, and have aided greatly in the establishment of the rôle of the gastro-intestinal tract in some microcytic anemias. Such information has also led to a rational therapeutic classification of the anemias.

The classic description of the patient with pernicious anemia has long included many characteristics which may make diagnosis by inspection from the foot of the bed possible. The rather well nourished lemon-tinted individual with blue eyes, fair complexion and prematurely gray hair is familiar to all of us. And further, the rarity of the disease in dark-skinned peoples and tropical residents has added to the conviction that a certain diathesis may underlie the development of this disease. Pernicious anemia is rare in Egyptians. Orientals[3,4] are peculiarly immune to its ravages. Negroes[5,6] seldom develop the disease. Only once was it diagnosed in approximately 8500 negro admissions to a large metropolitan hospital. At the Charity Hospital in New Orleans, however, Jamison[5] found its incidence somewhat higher. Many doubt its occurrence at all in the full-blooded negro.

These interesting phases of pernicious anemia have prompted Friedlander[7] to analyze 500 cases from the standpoint of constitutional types. His results confirm the greater frequency of the disease in white races,

especially in temperate zones, and further tend to show that within this group the light complexioned, fair-haired individual is most often affected. Percentage occurrence in Nordics was high. Dark complexioned and heavily pigmented patients almost invariably gave a history of fair complexioned ancestors or siblings.

The evaluation of such a factor, especially since many patients do not fit the constitutional type, is so bound up with the complexities of heredity that until analyses reach a mathematical stage, one must be satisfied with generalizations.

Barron[8] states that seldom do pernicious anemia and tuberculosis occur together. Those with pernicious anemia are practically free from tuberculosis, and on the rare occasions when the two diseases are associated, miliary tuberculosis is somewhat more common than other types. When associated in the same patient, each disease appears to run a course entirely uninfluenced by the other. To Barron the infrequent association of the two processes means antagonism. On the other hand, there appears to be an association between diabetes mellitus and pernicious anemia. Watson[9] regards the relationship as more than coincidental. In 24 of 31 cases, Root[10] noted the occurrence of diabetes before the onset of the anemia. Watson also noted this relationship. Possibly the effective therapy now in use in both diseases has increased the occurrence of the two simultaneously. Both, as well, have important hereditary aspects. Certain diabetics follow diets which could easily be inadequate in elements necessary for proper hematopoiesis, especially in the presence of altered gastric secretion often seen in diabetes.

The literature contains many data tending to demonstrate an interrelationship between pernicious anemia and idiopathic hypochromic anemia.[11] Heath has described a family with what he believes to be an inherited tendency to reduced gastric function. Pernicious anemia and idiopathic hypochromic anemia were both present in 3 sisters, and other members of the family displayed borderline cases of both macrocytic and microcytic anemia. Reports[12] are on record of the transition of the microcytic anemia into a macrocytic type.

When Castle[13] published his epoch-making observations demonstrating the presence in the gastric juice of normal individuals of an hitherto unknown substance, the intrinsic factor, which in the presence of certain foods, notably beef protein, an extrinsic factor, yielded a product which on absorption into the blood stream caused a remission in pernicious anemia, the way for an intelligent understanding of macrocytic anemia was cleared. The intrinsic factor was shown to be related to no known substance in normal gastric juice. Storage of this product, or one derived from it, appeared to occur in the liver. Thus, not only was it possible to correlate intelligently the efficacy of such preparations as hog stomach and liver in the treatment of pernicious anemia, but the relationship of many conditions producing the pernicious anemia blood picture could then be worked out.

Castle and his associates[14,15,16] define pernicious anemia as a deficiency disease conditioned by the lack of a specific factor. They describe three reactions by which macrocytic anemia may be produced: 1, pernicious anemia due to a lack of the intrinsic factor; 2, sprue, and at times pernicious anemia, mainly due to a lack of the extrinsic factor;

and 3, pernicious anemia due to defective absorption or utilization of the product of interaction of the intrinsic and extrinsic factors.

One is easily confused by the diversity of opinion regarding the nature of the extrinsic factor. Not only does it occur in beef muscle, but it has also been demonstrated in many other foods such as liver and liver extract, rice polishings, autolyzed yeast and eggs. The statement by Castle in 1932 that the extrinsic factor was vitamin B_2 and a subsequent communication,[14] that the reactions of the extrinsic factor correspond to those of vitamin B_2 have led to considerable investigation of the subject. Wills[17] and Wills and Naish[18] were unsuccessful in their attempts to confirm the views of Castle. Lassen and Lassen[19] were also unsuccessful in demonstrating a relationship to the vitamin B complex and an editor's note in their paper quotes Castle as being prepared to relinquish his views. Miller and Rhoads,[20] however, feel that the small amounts of vitamin B used in Wills' observations make her work inconclusive. By incubating 100 gm. of egg white containing 20 rat units of vitamin B_2 with 150 cc. of normal human gastric juice, reponses were obtained. Similar results were obtained with rice polishings, a substance with a known high content of vitamin B.

With such conflicting evidence one can but conclude that the question is still an open one. Whether or not the extrinsic factor is the vitamin itself, it is found uniformly in foods rich in the vitamin B complex.

No more settled than the identity of the extrinsic factor is the nature of the intrinsic factor. It is thermolabile and according to Castle's theory, requires a substrate (the extrinsic factor), properties which are usually identified with enzymes.[21] Contrariwise, the work of Morris[22] has demonstrated its ability to withstand the chemical treatment known to destroy enzymes. It is dialyzable and exhaustible, observations which have led Morris to the hormonal concept ("addisin"). The work of Greenspon[21] favors the latter view. The nature of the intrinsic factor remains, then, an unsolved problem of hematology and gastro-enterology.

Since the nature of both the intrinsic and extrinsic factors is unknown, it is not surprising that the nature of the product of their interaction, the hematopoietic factor, is also unknown. As with the building stones which allegedly produce it, attempts to purify, isolate and identify the principle have not met with success. Nevertheless, results of the investigation of its chemical nature have been most interesting. The work of Cohn is too well known to warrant further comment. Recently Kyer[23] and Subbarrow, Jacobson and Fiske[24] have attempted to isolate the active principle by adsorption on charcoal, and later elution with alcohol. By chemical manipulation the latter group has fractionated the active principle so obtained. Three fractions were obtained, two crystallin in nature. Although each alone was inactive, mixtures were highly active clinically. The relationship of these fractions to the intrinsic and extrinsic factors is obscure.

In their most recent observations, Dakin and West,[25,26] starting with commercial liver extract, have succeeded in obtaining a product 30 mg. of which causes a perceptible retoculocyte response and 80 mg. a maximum response in patients. The method of purification differs fundamentally from that of Subbarrow, Jacobson and Fiske. Inactive material was removed by precipitation with alcoholic calcium acetate

followed by precipitation of the active material with Reinecke acid. Further purification was done by a salting out process. Chemical analysis of the product obtained by Dakin and West and that of Subbarrow, Jacobson and Fiske shows marked differences, for example, in nitrogen content, differences which are dependent, no doubt, upon the two methods of purification and upon the fact that neither product is a pure one.

The theory of Castle has not gone unchallenged. At least four groups have raised objections.[21,22,27,28,29] The work of Castle swept into the discard the theory of toxins and toxic products as a cause of pernicious anemia. A renewal of interest in this theory appears to be arising with the reports of European observers[30] of success in production of remissions in pernicious anemia by the intravenous injection of Congo-red. The reported confirmation of these methods by Mermod and Dock[29] in this country led the latter observers, because of known neutralizing effects of Congo-red on toxic agents, to suggest a further exploration of the toxic theory. The demonstration by Wakerlin and Bruner[31] of a toxic reticulocyte depressing factor in the urine of patients with pernicious anemia in relapse adds weight to the suggestion of Mermod and Dock. Macht and Gardner's[32] demonstration of the phytotoxic action of pernicious anemia serum, persisting even in the stage of remission, lends further support to the toxic hypothesis.

While Mermod and Dock obtained reticulocyte responses in guinea pigs with Congo-red, therapy with this dye in clinical pernicious anemia was not carried to full remission. One must remember, too, that reticulocyte responses occur to many products given parenterally in the absence of the specific response as seen to liver in pernicious anemia. In recent reviews of the interpretation of reticulocyte responses by Minot[33] and Minot and Castle[34] emphasis is laid upon the fact that such reponses to liver therapy in pernicious anemia "are orderly and simulate the curve for growth and death of organisms and their cells." Such characteristics are necessary to proper interpretation and one should be hesitant in interpreting reactions not conforming to these characteristics as specific.

As previously stated, Morris and his co-workers published evidence to show that a gastric hormone or enzyme, "addisin," acts as a stimulus to hematopoiesis in pernicious anemia without the necessity of an extrinsic factor. This substance is supposedly diminished or absent in pernicious anemia. Whereas Conner[35] reported confirmation of Morris' work, Fouts, Helmer and Zerfas[36] were unable to isolate addisin by ultrafiltration unless some change has taken place in the gastric juice. Storage in the ice box for 2 months followed by concentration by ultrafiltration produced an active product, as did fresh gastric juice concentrated by vacuum distillation.

Three possible explanations for the results are given: 1, There may be interaction of an intrinsic and an extrinsic factor. Although the extrinsic factor has not been demonstrated in human gastric juice protein substances could act in this way. The fact that signs of muscle destruction are absent at the site of injection and that fresh gastric juice concentrated by ultrafiltration is inactive is against an interaction occurring at the site of injection. 2, The possibility exists that reticulocytes may have been produced by toxic substances. The observations of Minot have already been cited that reticulocytosis

may result from parenteral products, such as Fowler's solution and nonspecific proteins. According to Minot, such responses are usually prolonged and without orderly progression, not unlike those of Morris and Fouts, Helmer and Zerfas. Fouts recognizes the unusual character of the reticulocyte responses observed by him and his associates. 3, The third possibility is the activation of a gastric hormone. The data do not support this supposition.

Morris[37] also suggested that an excess of addisin, "hyperaddisinism," might explain erythremia and that gastric lavage is rational therapy for this condition. The evidence of Briggs and Oerting[38] and Kraemer and Asher[39] in carrying out this manipulation is not conclusive. Furthermore, it is very unlikely that the gastric principle does any more than add a factor which is necessary to permit maturation of the red blood cells. Oxygen tension of the bone marrow, not a gastric principle, appears to be the normal stimulus to red blood cell production. Were the gastric principle the stimulus, excess liver extract would necessarily produce polycythemia, a condition not seen in overdosage.

In the interpretation of Bloomfield and Polland[28] the theories of Castle play a narrow and restricted rôle in hematopoiesis. These authors have followed a group of individuals with unexplained gastric anacidity for periods varying from 1 to 12 years. There was no suggestion of the development of pernicious anemia. Attempts to demonstrate Castle's factor in several cases of anacidity without anemia failed.[40] Quantities of hematopoietic factor found in the low-volume mucoid secretion of such patients hardly seemed sufficient to keep blood values normal. Says Bloomfield, "All this to our minds indicates that the absence of Castle's intrinsic factor in gastric juice does not necessarily lead to the development of pernicious anemia." Only an occasional person requires such protection. Rarely following gastric resection does macrocytic anemia develop. In carcinoma of the stomach the anemia is usually microcytic. Desiccated dog stomach[41] is only one-half as effective as that of swine.

Greenspon[21] adds a new interpretation to the results of Castle's experiments in his postulation of a theory quite similar to that of Morris. Greenspon believes that the hematopoietic response results from the activity of a gastric hormone without the necessity of an extrinsic factor. His experimental data show an hematopoietic response to gastric juice when peptic activity is destroyed or prevented by alkali or cold temperatures. Pepsin, he states, has a strong affinity for protein which adsorbs it from a fluid medium. Depepsinized but otherwise normal gastric juice without an extrinsic factor was found to be effective in therapy. The beef in Castle's basic experiment supposedly adsorbs the pepsin which then cannot destroy the hematopoietic principle. The effectiveness of ventriculin is ascribed to the inactivation of pepsin by the muscularis. It is possible on the other hand, that the extrinsic factor under attack was not completely excluded under the condition (FitzHugh[42]) of Greenspon's experiments.

Greenspon's theory, as yet not confirmed, appears from the data given to explain adequately anemias classified by Castle as due to a loss of the intrinsic factor. A consideration of the anemias due to a loss of extrinsic factor alone finds small place in the interpretations of Greenspon. In such cases his explanations are weak indeed. He suggests

the possibility that the substance containing the so-called extrinsic factor includes factors which stimulate cells of the stomach or furnish elements for synthesis.

If the intrinsic factor is absent in patients with pernicious anemia, why do any red blood cells mature at all? Why should various patients have in relapse varying red blood cell levels? Such questions have stimulated Goldhamer[43,44,45] to a study of these aspects of the disease. Castle had noted[15] a reappearance of the intrinsic factor in 1 patient following use of liver extract and suggested that the defective production of the intrinsic factor is relative and not absolute. Goldhamer's results support this statement. He collected gastric juice from 26 patients with pernicious anemia in relapse. Secretion averaged 20 cc. per hour as compared with 150 cc. for the normal. Repetition of Castle's experiment with this gastric juice in quantities comparable to those of the normal individual gave responses suggesting that patients with pernicious anemia do secrete the hematopoietic factor but in deficient quantity. A direct relationship was found between the volume of gastric juice and the red blood cell level in relapse. It is conceivable that a defective supply of extrinsic factor might, in a patient with a reduction of the intrinsic factor to a critical level, precipitate anemia. Such a mechanism may explain the response of some patients to autolyzed yeast,[46,47] especially since these products are not effective parenterally.[48]

To state simply that pernicious anemia is usually due to a loss or deficiency in the intrinsic factor seems simple enough. But why is it absent or deficient? The cause is apparent in gastrectomy, polyposis and carcinoma of the stomach. But the why of its absence in true pernicious anemia is seldom the topic of investigation. The work of Miller and Rhoads in demonstrating the disappearance of the intrinsic factor from the stomachs of experimental animals on vitamin B deficient diets appears to concern itself more with the pathogenesis of sprue and pellagra than with pernicious anemia. The possibility of a constitutional factor has already been discussed. The work of Bloomfield and his associates correlates well with this view. The reduced volume of secretion with achylia gastrica is probably very important in the light of Goldhamer's observations. That the principle may or may not occur in achylia[49] indicates that it alone is an insufficient explanation. The absence of the intrinsic factor in the presence of free hydrochloric acid[50] demonstrates the lack of dependence upon the acid factor.

The extensive observations of Castle and his associates upon patients with sprue[50] demonstrate its intimate relationship to pernicious anemia. The same systems (nervous, gastro-intestinal, hematopoietic) are involved in both diseases. Castle states that at times, "It was beyond our clinical ability to decide whether the condition under observation in Puerto Rico was sprue or pernicious anemia." Patients demonstrated an interference with one of all three mechanisms possible in the development of macrocytic anemia. Sometimes the extrinsic, sometimes the intrinsic factor was lacking while in other cases absorption from the intestines was the important defect. Recently Miller and Rhoads[51] have demonstrated roentgenographic changes in the small intestine in patients with sprue. A return toward normal form and function

followed the injection of liver extract, suggesting that liver extract parenterally conditions the functional activity of the small intestine.

Pellagra, as well as sprue and pernicious anemia, involves the gastrointestinal, nervous and hematopoietic systems. The work of Miller and Rhoads[52] on the effect of vitamin B_2 deficient diets upon swine may be recalled here. Stomatitis, gastric anacidity and a macrocytic anemia amenable to liver therapy, resulted. Spies and Payne[49] have shown the presence of the intrinsic factor in the stomach of pellagrins with achylia gastrica. The association of vitamin B_2 with the extrinsic factor and its place as the alleged cause of pellagra gave promise in associating the two diseases. The work of Spies and Payne,[53] however, speaks against such an association. In demonstrating that pellagrins improve on yeast, which when incubated with normal gastric juice, caused no remissions in patients with pernicious anemia, they suggest that the chemical substance in yeast utilized by the pellagrin to remit his disease is not the same as the precursor of the anti-anemic factor in food.

A fourth mechanism for the development of macrocytic anemia appears evident in the association of cirrhosis of the liver with macrocytic anemia. While such an association has been known for years, it remained for Wintrobe and Shumacker[54] and Van Duyn[55] to re-awaken interest in the subject. The occurrence of free hydrochloric acid in the gastric contents of these patients speaks against a mere association of cirrhosis and pernicious anemia. Such patients, then, are capable of producing and adsorbing the hematopoietic factor; but, because of liver disease, they are either unable to store or further elaborate upon the principle. Goldhamer, Isaacs and Sturgis[105] suggest that the liver may be sufficiently damaged so that the principle, although present, cannot be presented to the tissue for utilization. Its absence has been demonstrated in the cirrhotic liver.

Van Duyn[55] has suggested that the patients with macrocytic anemia and free hydrochloric acid should be suspected of liver disease. He regards this combination of findings as a sign of hepatic dysfunction. Such findings could be present as well in the macrocytic anemia of gastric syphilis or polyposis, intestinal stenosis and sprue.

A number of negative findings of interest have been reported recently. Stare and Thompson[56] can attach no significance to the flavines in pernicious anemia. Alt[57] finds only hypochromic anemia in experimental goats' milk anemia. Previous reports have described this anemia as hyperchromic. Watson,[58] having in mind the demonstration by Hans Fischer of increased coproporphyrin in the urine of patients with pernicious anemia in relapse, isolated this substance from the feces of similar patients. While coproporphyrin has been identified in Germany with the erythroblasts and megaloblasts of pernicious anemia marrow, its significance remains unknown. The fact that it occurs in brewers' yeast, and is increased by autolysis suggests a possible relationship to the extrinsic factor. The American literature shows no investigation of this aspect of porphyrin metabolism. Helmer, Fouts and Zerfas[59,60] found no correlation between the pancreatic enzymes and the maintenance dose of liver extract. Goldhamer[61] has found that the retarded rate of glycolysis in pernicious anemia is proportional to the red blood cells decrease. He finds that an increase in

the rate of glycolysis per hour per million red blood cells in early remission is associated with an increase in reticulocytes.

Pathology. Postmortem observations, such as those of Brown,[62] have demonstrated a great variety of morbid changes in the gastrointestinal tract of patients with pernicious anemia. In Brown's series of 151 cases, 60 showed evidence of old intraabdominal infection, and, in all cases but 1, microscopic evidence of chronic inflammation was found. Chronic gastritis occurred in 41 of 42 specimens studied microscopically. Adhesions and partial intestinal obstruction were frequent findings.

Although achylia gastrica has long been described as an invariable accompaniment of Addisonian pernicious anemia, note has already been made of occasional exceptions to this rule. Most studies of the gastric state in pernicious anemia have been carried out postmortem. Recent observations by Jones, Benedict and Hampton[63] in living patients by gastroscopic, roentgenologic and direct observation at operation demonstrate that, contrary to generally accepted views, atrophy of the stomach is not an invariable accompaniment of pernicious anemia. Under adequate liver therapy over a period of months, all evidences of atrophy disappeared in 2 cases with a return to a normal appearance. Tissue sections at operation were confirmatory. An hypertrophied stomach was noted in 1 case and all showed evidence of chronic inflammation.

Heck and Watkins[64] describe a "shift to the right" in the neutrophil of pernicious anemia. Exceptions were encountered, however, in which a shift to the left was found. No relationship of hypersegmentation to the degree of anemia was observed. Finer structural changes in the nuclear skein were also noted.

Symptomatology. Greatest interest in the symptomatology of pernicious anemia lies at the present time in the field of neurology. Such rare associations as the Parkinsonian syndrome with pernicious anemia deserve little comment. Brain tumor may be simulated even to the occurrence of papilledema.[65,66]

There is great diversity in the statistics recorded by various authors as to the frequency of spinal cord and cerebral symptoms. For example, cerebral symptoms are reported in from 4 to 64% of patients.[67,68] Such great variations mean, no doubt, differences in criteria for their recognition. Most symptoms of cerebral origin are those usually found and included in the term toxic psychosis. Hallucinations, apathy, delusions, stupor and symptoms resembling the more important organic psychoses are present. Diversity of opinion lies not only in the expression of such symptoms but also in their relationship to the pernicious anemia. Tenny and Goldstein[68] are of the opinion that familial and personal predispositions are important factors in their production. Osgood,[69] as well, concludes from 17 cases analyzed that the association of psychoses with pernicious anemia is probably largely incidental. On the other hand, Parfitt[70] and Preu and Geiger[71] believe that, through toxemia or actual organic lesions, pernicious anemia is directly responsible for the psychotic manifestations. The latter observers attribute the differences in interpretation and incidence of the symptomatic psychoses to the failure of the internist to apply the established criteria

of psychiatry to these patients and a similar failure on the part of the psychiatrist to recognize the accompanying anemia.

The incidence of cord changes is reported much higher than the incidence of cerebral changes. Goldhamer, Bethell, Isaacs and Sturgis[67] found 364 out of 408 cases with neurologic changes. Of these, posterior column involvement occurred in 89.2%, lateral column involvement in 41.6%, and combined disease in 40.7%.

Diagnosis. The group of seemingly unrelated clinical states producing the pernicious anemia blood picture, for example pernicious anemia, sprue, celiac disease, multiple intestinal anastomoses and fish tape-worm infestation, although all having in common one factor, the involvement of some portion of the gastro-intestinal tract, defied adequate explanation of their relationship to each other until the work of Castle in 1929. Since then, as has been mentioned under Etiology, a classification of the macrocytic anemias according to mechanismal disturbance has been possible. Disturbances in pernicious anemia, sprue, pellagra and cirrhosis of the liver have already been mentioned. In the macrocytic anemias of gastric syphilis and carcinoma, polyposis of the stomach and gastrectomy, the pathogenesis is evident. In intestinal adhesions, anastomoses and stenoses and in the diarrhea of celiac disease, a disturbance in absorption suggests itself. All patients showing the pernicious anemia blood picture deserve study for the presence of one of these detectable disturbances, cure of which may lead to permanent remission of the anemia. This is especially true in the presence of free HCl in the stomach, as suggested by Van Duyn.[55] Although Van Duyn regards the presence of macrocytic anemia and free HCl in the stomach as a sign of liver dysfunction, it may be used as a sign indicative of macrocytic anemia associated with gross gastric disease or extragastric disease which may be capable of correction.

The diagnostic approach of Beebe and Wintrobe[72] to doubtful and obscure cases of pernicious anemia is worthy of repetition. The gastric juice of the suspected case, when incubated with ground beef, is compared in its effects with that of known individuals when fed to known cases of pernicious anemia in relapse. The test is described as of diagnostic assistance 1, when arteriosclerosis, infection and chronic disease make the response to therapy inadequate; 2, in cases of damage to the spinal cord with little or no anemia when the blood does not make the diagnosis and 3, in patients with little anemia, receiving liver, and in whom, if treatment were stopped for diagnosis, nervous symptoms might develop.

Treatment. Most patients with pernicious anemia may be treated adequately by the ingestion of liver. However, monotony of diet and distaste for liver, together with scientific inquisitiveness, have led to the development of many concentrated preparations of liver extract available commercially. Since therapeutic effect is dependent upon proper standardization of dosage the method of assay becomes most important. In the absence of the purified principle, assay depends entirely upon biological effects, and in this instance upon the reticulocyte response.

Attempts have been made to free the assay of liver products from dependence upon patients in relapse. Laboratory animals, especially guinea pigs and pigeons, have been used for this purpose. Jacobson[73,74]

in controlling the variables of diet and environment in the guinea pig, and with the use of control periods, reports the demonstration in picked animals of reticulocyte responses, a quantitative expression of hematopoietic activity being recorded as guinea pig units. Such assays conform with expected results[75] with the liver of patients with pernicious anemia in relapse and in remission, as well as with the liver of non-anemic patients.

On the one hand, the work of Jacobson has been confirmed,[76] on the other hand, Goodman, Geiger and Klumpp[77] report responses similar to those of Jacobson after normal saline alone. They interpret all their reactions as spontaneous or non-specific.

Attempts to use as test animals pigeons on an inadequate diet to decrease the percentage of circulating reticulocytes have given results[78] indicating wide fluctuations in percentage of reticulocytes without significant effects by the test substances. Such observations indicate clearly that for accurate therapeutic assay, we must still rely upon the patient in relapse.

Minot's interpretations of reticulocyte responses have already been noted. He states further that the character of the reticulocyte response varies with: 1, the initial red blood cell level; 2, the amount of active material given; 3, the portal of entry; 4, the rate at which the materials enter the body and, 5, the reactive state of the bone marrow. The initial red blood cell level is most important in biological assay. Reticulocyte responses expected with full dosage of active potent material have been worked out for the various initial red blood cells levels below three million. Bethell[79] and Bethell and Goldhamer[80] have shown that the reticulocytes bear an inverse relation to the number of red blood cells. Mathematical expressions of these relationships have been formulated for both oral and parenteral administration. Recent establishment of such criteria for potency of liver preparations by the Council on Pharmacy and Chemistry of the American Medical Association[81] places the commercial preparations so approved upon standards which assure the physician of the potency of the material used.

There have been three well known methods used to increase the potency of liver. Methods of concentration such as that of Cohn, of Subbarrow, Jacobson and Fiske, and of Dakin and West have already been considered. Increased potency has also been claimed by liver autolysis. By this method Herron and McEllroy[82] claim to have produced a preparation with an oral dose approaching that of the parenteral route. A commercial preparation was offered to the profession upon the basis of this work. Castle and Strauss,[83] however, found that with both experimental and commercial autolysates less hematopoietic activity resulted than with comparable amounts of liver from which they were derived. Their analysis of Herron and McEllroy's cases does not support the reported conclusions. Klumpp's results[84] are in complete agreement with those of Castle and Strauss. He found, however, that the autolyzed liver is effective in the initial and maintenance treatment of pernicious anemia and that the autolyzed liver concentrate was more potent than a commercial extract derived from the same amounts of liver. Conner and McQuiston,[85] from their results with autolyzed liver, state that "It seems justifiable to say that the preparation which we used in clinical trial (commercial preparation) is not

reliable in the dose recommended and in some cases it is not reliable in even double this dose. It seems that it cannot be said definitely that autolysis either increases or decreases the effectiveness of liver in the treatment of pernicious anemia."

The third method in use for increasing the potency of liver preparations is digestion with normal gastric juice. First carried out in Europe with whole liver, the procedure has been repeated in this country both with whole liver and liver extracts. Although Barnett and Thebaut[86] were unable to obtain positive results the subsequent work of Walden and Clowes[87] and Fouts, Helmer and Zerfas[88–91] demonstrates conclusively a marked increase in potency of extracts so treated. Assays were carried out upon clinical cases of pernicious anemia. Maximal reticulocyte responses were produced only when definite amounts of gastric juice and liver extract were used. Fouts and his associates believe that the increase in potency is a result of the type exemplified by the interaction of beef muscle and gastric juice rather than an actual increase in the active principle originally present in liver.

The production of active preparations suitable for parenteral use has led to a widespread adoption of this form of therapy. McHenry, Mills and Farquharson,[92] although finding the potency of intramuscular extracts approximately thirty times that of oral products, find no better results than with adequate oral therapy. Parenteral therapy is distinctly advantageous in those patients in severe relapse or those refractory to oral therapy.

There are distinct advantages to intramuscular therapy. Murphy[93] enumerates the advantages as 1, certainty of dosage under absolute control; 2, rapid response in severe relapse; 3, response of "resistant cases;" 4, efficacy of treatment in combined system disease; 5, convenience of infrequent injections in uncomplicated cases; 6, economy in the cost of material; 7, the freedom of the patient to travel. He[94] has found it possible to maintain patients upon extracts from 100 gm. of liver with injections at 1 to 6-week intervals. Sherman[95] has spaced doses at weekly intervals but was unable to determine the exact dosage before treatment. Others as well[96–99] have been able to space injections as infrequently as 1 month apart in some cases. Individual variations in patients, however, are most important in the determination of the proper amount and the spacing of medication. Intravenous products[98,99] have been successful in preliminary studies but as yet are undesirable for routine treatment.

The method of Haden[100] for the determination of adequacy of treatment is both simple and satisfactory. Since glossitis and parasthesias may disappear and the blood values may be above the accepted lower limits of normal, yet submaximal for the individual under consideration, the red blood cell count alone is unsatisfactory. Haden believes that macrocytosis supplies a sensitive indicator of adequacy of treatment. "This is the first hematologic manifestation of the disease and persists when all other signs are gone, so is by far the most valuable indicator of the deficiency." Absence of macrocytosis, then, indicates complete remission.

The greatest controversy in the treatment of pernicious anemia lies not in the hematologic response but in the response of neurologic changes. Reports are most conflicting, due in part according to Garvey,

Levin and Guller[101] to the variations in criteria used. Subjective findings often improve with therapy. These, too, may be difficult to evaluate in a patient with cerebral symptoms. Also, subjective findings are inherently difficult to classify.[98] Spontaneous variations in the absence of treatment may add further confusion to interpretation. There are those[68,97] who believe that liver therapy may not only arrest the progress of nervous manifestations but may actually cause objective signs to disappear. Most authors[67,98,101,102,103] are less optimistic. Farquharson[103] reports complete arrest of the progress of the neurologic manifestations in all patients taking the prescribed amount of liver and improvement in neurologic symptoms especially if of short duration. Best results were obtained with intramuscular liver. Adequate dosage is described as the amount required completely to arrest progress of the lesion. Since such doses cannot be predicted, Farquharson suggests the use of two to three times the dose commonly used without cord lesions. Mills' results have been somewhat similar.

Fouts and Zerfas have observed patients in whom large amounts of liver extract were insufficient to prevent progress of nervous involvement. Grinker and Kaudel believe that liver is not effective in preventing cord degenerations. Goldhamer, Bethell, Isaacs and Sturgis found improvement in symptoms in less than 50% of the cases and in signs in about 2% with adequate anti-anemic therapy. They believe that anti-anemic therapy does not have a specific curative effect upon spinal cord degeneration but contributes only indirectly to such improvement. The course of the disease in individual cases varied widely.

Strauss, Solomon, Schneider and Patek[104] list as reasons for failure of results to agree: 1, evidence of the effectiveness of treatment must be judged by the evidence of arrest of the process and not by the degree of improvement, for regeneration of destroyed spinal nerve cells cannot be expected any more in pernicious anemia than in tabes dorsalis; 2, the improvement in the neurologic state may be entirely due to improved general health, reëducation and similar factors. Peripheral nerve changes may completely disappear; 3, cord lesions do badly in the presence of sepsis; 4, short observations may lead to abandonment of hope of improvement before adequate therapy is given. Their results indicated: 1, in no instance did an objective sign progress nor a new one appear; 2, subjective improvement occurred in all patients; 3, except for gait and paresthesias, about 58% of all abnormal signs were objectively unchanged.

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PEDIATRICS

UNDER THE CHARGE OF
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PREMATURITY AND IMMATURITY AS MEDICAL PROBLEMS.

According to Hess[1] a mature baby is one born at term, or at the end of from 270 to 290 days of gestation, irrespective of the degree of development of the baby. Classified as immature is any infant, whether

a single or multiple birth, born prematurely, at term or even past term, whose weight is below 2500 gm. ($5\frac{1}{2}$ pounds). Such infants are not completely prepared for full, normal, independent extrauterine existence. Premature infants comprise a large number of those classified as immature. A consideration of premature infants would not cover all of the problems of the undersized baby as there are many born in single birth beyond the average normal period of gestation which, because of their weight and size, must be considered in this category. There are also the majority of infants of multiple births who qualify for this classification.

The problem of the undersized and underdeveloped infant has received much consideration from the medical profession. Methods and apparatus for the care of these have been well established for many years. As a result, innumerable cases have been reared successfully by the physicians of this and other countries. Although the presence of a problem of this sort would hold the interest of the family and closer circle of friends, as a rule, the general public has been unaware of these cases except in unusual instances. The reward of the host of doctors, who have participated in the direction of the care of these babies, has been found in their own satisfaction in the results. The multiple delivery resulting in the birth of the 5 female babies, now famous as the Dionne quintuplets, has centered the interest of the world in their problem, and has aroused professional and lay interest in the protection and care of the subnormal baby. Through the interest manifested and by means of the funds secured from various sources, it has been possible to crystallize around these sisters all of the worthwhile developments of previous decades.

Early in the consideration of this subject the question arises as to the frequency with which immature and premature babies are seen. Inquiry was made to several national and federal agencies. From the lack of reply on this point it is presumed that such figures are not available. The certificates of birth in use do not require information on this point. The only statistical data available are the mortality figures for premature infants, as arranged by Dunn[2] as follows:

Death and death rate per 100,000 estimated population from premature birth in United States, 1930–1934.

Year.	Deaths.	Rate.
1934	35,102	*
1933	32,953	26.2
1932	33,143	27.6
1931	34,477	28.9
1930	37,433	31.6

* Not available.

Dr. E. C. Tandy[3] summarized these figures as follows: "The number of deaths under 1 year from premature birth in the United States in 1933 was 32,953, and in 1934, 35,102. The majority of these deaths occur in the first month of life. In 1933, 31,796 occurred during that age period." From a table furnished by her, based upon Bureau of Census figures, are noted on page 142.

Year.	Death under 1 month.	Rate per 1000 live births.
1921	27,932	16.8
1922	26,835	17.0
1923	26,816	16.7
1924	27,409	16.7
1925	26,075	16.4
1926	26,334	17.0
1927	25,300	16.2
1928	25,273	16.7
1929	24,149	16.5
1930	23,204	15.7
1931	21,426	15.3
1932	20,629	15.1
1933	19,718	15.3

These figures show a tendency toward a decrease in the total number of deaths of premature babies during the first month of life. The mortality rate of such deaths per 1000 living births has fallen in a period of 12 years from the highest rate of 17 to 15.1. When the number of deaths during the first month of life is compared with the total number of deaths of premature babies for the years that such figures are available, it is seen that the great preponderance of such deaths occur in the first month. Premature and immature babies that can be carried beyond this age have far better and increasing chances of surviving. Although there has been a decided decrease in the mortality rate for this age period of premature babies as shown in the above table, the toll is excessively high.

On the basis of the generally accepted classification of prematurity on a weight of less than 2500 gm., Milio[4] studied 1000 deliveries. The majority of the infants were born between the 270th and the 290th day of pregnancy. The majority of the infants born during the usual physiologic limits of pregnancy weighed from 3000 to 3500 gm. and were considered as normal. A considerable number weighed less than 2500 gm. and were imperfectly developed organically and functionally, or immature. In such babies the intrauterine life, although it may have been within the normal limits, had not been sufficiently long for these infants to mature. On the other hand, some of the babies in pregnancies shorter than 270 days were of the normal birth weight and apparently mature. Therefore, there must be some other elements besides the length of gestation which determine whether or not the baby is to be normal in size and development. About 12.9% of the 1000 cases studied by Milio weighed less than 2500 gm. This included only those born alive. He found that the following were the causes of the immaturity: "In 21 per cent, renal disease of the mother; in 16.2 per cent, multiple birth; in 15 per cent, diseases and anomalies of the organs of parturition and of the sexual organs, and in 11.6 per cent syphilis of the mother." Other causes were acute infectious diseases, diseases of the heart, tuberculosis and anemia of the mother. He could find no explanation in 21% of the cases of his series.

Hilgenberg[5] observed in his clinic, between 1925 and 1930, 4368 deliveries. There were 214 living children weighing less than 2500 gm. This was an incidence of prematurity of 20.4%. Of these, 20% died before the age of 10 days. According to Clifford,[6] the premature group

represents about 3% of the total births, but contributes one-half of the total neonatal deaths. Over 80% of the premature fatalities occur during the first 48 hours after delivery and pediatric care is without avail in preventing these deaths. He urged that this mortality can be reduced by delaying induction of premature labor whenever possible until a viable baby can be assured. His method is to make an estimation of the weight of the fetus *in utero* through mensuration of the occiptofrontal diameter of the fetal head by means of a modified roentgenometric technique. From this diameter the expected body weight can be judged. In the severer grades of toxemia the situation may arise wherein it is safer for the fetus to take its chance of being delivered as a premature infant than to run the risk of being stillborn if the pregnancy should be allowed to continue. The risk to the fetus in prematurity can be determined from information as to its expected birth weight. The expectation of premature death is in direct proportion to the difference between its weight and the average normal weight of a full-term baby. The smaller the baby the more likely is it to die. The old idea that 7-month babies are more apt to survive than those born at 8 months, is not borne out in fact. It is necessary, therefore, to consider the estimated weight of the baby against the severity of the toxemia in order to come to a decision. In pregnancy complicated by heart disease without failure of compensation, there seems to be little danger of intrauterine death of the fetus and pregnancy should be allowed to continue as far as the maternal condition will permit, but it is important to the future of the fetus that delivery should not be delayed until congestive failure develops, for this is another cause of high infant mortality. According to this author, the influence of knowledge as to the weight of the fetus *in utero* in the management of certain types of pregnancy has contributed to the reduction of the stillbirth rate to 47 in 1933 from a level of 69 per 1000 deliveries for the preceding 10 years. It has been instrumental in increasing the incidence of premature babies born alive from an average of 27.6 for the preceding 10 years to 34.7 per 1000 deliveries for 1933. The proportion of premature babies weighing from 4 to 5 pounds at birth increased from an average of 52% for the preceding years to 61% during 1933. The premature infant mortality dropped for the first time in 5 years from 35 to 29%.

Litchfield[7] endorsed the opinion that syphilis is in large measure a primary factor in causing premature expulsion of the fetus. In his clinic there were found 56 stillbirths of which 40 had positive Wassermann records. Of these 40, 6 had a 4+ cord Wassermann. Autopsies on 21 other stillborn babies showed definite syphilitic lesions in 9.

Among other conditions during delivery requiring consideration, atelectasis is important. McGrath and Kuder[8] performed resuscitation on 21 premature babies delivered by them; 13 died; 11 were examined postmortem and all showed atelectasis except 1. Another frequent cause of neonatal death of the premature is intracranial hemorrhage resulting from trauma during birth. Hilgenberg (*loc. cit.*) pointed out that in the underdeveloped infant the vascular walls tear very easily and cause congestion of the blood when subjected to force owing to the deficient development of the elastic fibers. Premature children also suffer more often from intracranial hemorrhage because of their

small size and the compressibility of their skull. The diagnosis of intracranial hemorrhage in the premature is extremely difficult for the reason that almost every premature baby presents the same picture as that of an infant with intracranial hemorrhage. Bonar[9] stated that the diagnosis of intracranial hemorrhage of the newborn is based upon the symptoms of increased intracranial pressure. Minor hemorrhages are the most difficult to detect. Somnolence is the rule, although some infants are hyperirritable. In these the distressed or cephalic cry may be heard during sleep. Other signs are nystagmus, transient palsies of the eye muscles and minor cyanotic attacks. The two most important, but often unrecognized symptoms, are continued intermittent protrusion of the tongue (Foote's sign), and refusal to nurse. In the severe forms cyanotic attacks are more common, and there may be twitching of the facial muscles, increased muscle tone, rigidity, choreiform motions or athetosis, and even convulsions, as well as bulging of the anterior fontanelle.

The viability of premature infants is a mooted point. It is difficult to correlate for consideration in any particular case all of the factors for and against survival in the inheritance, in the infant itself and in the environment. However, there appear in the literature from time to time reports of the survival of very young and very small individuals. Fischer-Ban[10] recorded the survival of an infant of $6\frac{1}{2}$ months' gestation, weighing 600 gm. According to her, the previous low weight record with survival was 680 gm. This child received teaspoonful doses of tea for the first 12 hours, and after that a teaspoonful of breast milk every 2 hours. After the 8th day it was fed breast milk from a bottle and it was able to suckle at 3 months.

The question of the anemias of prematurity has engaged the attention of a number of observers. Josephs[11] studied a group of premature babies during the first 3 or 4 months of life. He attempted to determine the mechanism of the so-called physiologic anemia of prematurity. From his study of the reticulocytes he concluded that there is no basis for the idea that the fall in the red cells and hemoglobin was depended on hypoplasia in any strict anatomic sense. There was a period of failure to react to the administration of iron that lasted from 6 to 10 weeks after birth, the duration of the period depending on the degree of prematurity. After this early period of non-reactivity there follows a short transitional period, after which administration of iron was followed by a prompt response of reticulocytes with a rise in red cells and hemoglobin. There was no reason to believe that lack of stores of iron played any part in the development or persistence of the anemia before the end of the third month. Thereafter the rise in red cells without a corresponding rise in hemoglobin in untreated infants indicated the possibility that lack of stores of iron had become an important factor. From the results reported in his paper it cannot be concluded that a low percentage of hemoglobin is in itself harmful, although probably it is indicative of a condition that renders the infant more likely to succumb to infection. In such cases, although iron may raise the hemoglobin content, transfusion must still remain the method of choice in treating the condition as a whole. The evidence from this study does not permit of the conclusion that liver is necessary as an adjunct of iron, though in individual cases it may prove of benefit.

The same of the problem of the premature has been the subject of contributions by Merritt and Davidson[12] and Abt.[13]

According to Lowenburg,[14] although the general principles necessary in the care of premature babies are well established and widely recognized, the application of these without individual discrimination will not be successful. A procedure applied successfully in 1 case may fail when applied in the next. This attitude of versatility toward the variations of the problems that appear from day to day or even sometimes from hour to hour is a prerequisite of success, especially in the very small baby. Among his recommendations are finesse of judgment, fine adjustment from day to day, and even the withdrawal or alteration of an order, if the reactions do not indicate that it is of benefit to the baby. In addition he emphasized intelligence and patience and the coöperation of a wise, calm and intelligent attendant.

Jewesbury[15] pointed out the distinguishing characteristics of the premature child. The undeveloped state of the nervous system not only makes it more sensitive to external influences but also causes an inability to regulate and to maintain body heat. The relative surface area of the body is larger than in the normal baby and there is also an absence of subcutaneous fat. The suckling and swallowing reflexes are feeble or absent and, therefore, the nutritional intake is low. The underdeveloped state of the digestive system makes it more difficult for the premature baby to deal with any food except mother's milk. If this is rich, it may be necessary to modify the concentration of this to meet the capabilities of the premature stomach. There is a general low state of vitality with a consequent lack of resistance to infection. The heart, the lungs or other organs may be defective or too underdeveloped to function properly. This is the exception rather than the rule. In managing the premature baby prenatal conditions must be continued as far as possible. The essentials are warmth, sufficient fluid and food of a suitable kind and protection from infection.

Infection is an important element in infant mortality without regard to maturity or prematurity. Obviously the latter increases the hazards. Grulee, Sandford and Herron[16] studied 20,061 infants from birth to 9 months of age. Of these, 48.5% were totally breast-fed, 43% partially breast-fed, and 8.5% artificially fed. The total morbidity of the breast-fed group was 37.4%, of the partially breast-fed group 53.8%, and of the artificially fed group 63.6%. The average mortality of these infants was 1.1%. Of this mortality, 6.7% were in the breast-fed group, 27.2% in the partially breast-fed group, and 66.1% in the artificially fed group.

Although the principles of the care of the premature baby are classical, it may not be amiss to review these with Jewesbury (*loc. cit.*). Special care must be taken from the moment of birth. The baby should be placed at once in a properly warmed receptacle. In order to minimize handling, it is recommended that the baby should not be oiled before 6 hours after birth, but the cord must be attended to in the regular manner. If the baby is very feeble, it should not be weighed. All the details of nursing, care and handling are exceedingly important, the main object being to conserve the baby's warmth and energy. At the outset the skin should be cleaned with olive oil every second or third day, until there is a steady gain in weight, after which the infant

should be oiled every day. When a weight of about 5 pounds has been attained, and then only if the baby is vigorous, a bath may be begun at first only every other day. The room temperature must be maintained at from 70° to 75° F., and when the baby is to be handled it is advisable to have even higher temperatures. In the maintenance of heat the cradle or basket is an important factor. Formerly incubators were used, but these have been found not to be essential. An electrically heated bassinette or a basket or cradle heated by some other means may be used. The source of heat and the method of securing this is not so important as is the necessity of regulating it to meet the varying needs of the infant. This is best judged by means of the temperature of the baby taken rectally. The clothing is an additional factor in the maintenance of the body heat. There are individual preferences as regards the clothing but Jewesbury's recommendations conform to the usual standards. He uses a binder of crepe bandage until the cord is off. A jacket is made by dividing Gamgee tissue and covering one side with gauze. This can be washed from time to time and is held in place better than the loose strips of wool or cotton that are sometimes used. A suitable petticoat and a woolly coat or sweater is used. The head should be covered with wool or a small woolen cap or bonnet. The feet and legs should always be kept warm and for this knitted woolen bootees that come well above the knees should be used. The napkin should be soft and not bulky and need not be fastened until the child begins to be active. During the early phase it may be preferable to use a triangle of sterile cotton batting. Over all of the clothing a soft woolly shawl or light blanket should be added, so arranged that a corner can be used to cover the head of the baby.

In addition to the maintenance of body temperature the problem of fluid and food is the earliest need. The daily requirement of fluid is from one-sixth to one-fifth of the body weight. The amount of food and the frequency of feeding depend on the age, size and digestive capacity of the individual baby. Sometimes it is necessary to give the fluid at 2 or 2½-hour intervals, and in rare cases more frequently, but the 3-hour interval is usually satisfactory. The longer intervals should be aimed at in order to give the stomach time to empty and in order to allow the child more rest. Breast milk is usually preferable. This may be obtained from the mother or from other sources, and its concentration modified as condition requires. Usually it is necessary to feed this indirectly by means of a pipet, Breck feeder or bottle, but as the child grows and gains in vigor it may be suckled.

Hess[17] also stressed that each premature baby is an individual feeding problem. He emphasized that vomiting and cyanosis are contraindications against increase in feedings. He stated that we must have a definite idea of the minimum food requirements for life. The amount of food necessary to maintain at least a stationary weight must be given, and in addition enough food to meet the requirements for growth and development. As soon as possible the feedings must be increased to from 90 to 100 calories per kg. of body weight per day and from one-sixth to one-fifth of the body weight in fluids as represented in the food and additional water. Under average circumstances this should be possible by the 10th to the 20th day. He recommended that from 140 to 180 cc. of breast milk per kg. of body weight daily should be

given. In Hess' Clinic skimmed lactic acid milk is added to the feedings of many infants. Such additions are started on the 4th or 5th day.

Lowenburg (*loc. cit.*) placed the daily caloric needs of premature babies at a minimum of 50 calories per pound daily and most of them at from 70 to 100 calories. He gave the fluid requirements as $2\frac{1}{2}$ ounces per pound of body weight per day. This amount should include the fluid given as such as well as that representing the feedings. Although he recommended the feeding of human milk, this author has found that evaporated milk is of great value in the care of the premature baby. He stated: "It truly represents *multum in parvo* in a digestible form. Prematures as well as other newborn babies have no difficulty in digesting evaporated milk, either diluted with water, with 5% glucose or with the hydrating solution of Kugelmass. It may be thoroughly digested, diluted or even entirely undiluted. Both cow's milk and human milk provide about 20 calories to the ounce, but evaporated milk represents 40 calories. Because of this additional food value one-half as much may be used in balancing the caloric needs of the baby. All sorts of combinations may be devised where individualization is most needed. In the babies that suckle well, have a fair stomach capacity and do not regurgitate, the problem of feeding is comparatively simple. Lowenburg rated tube feeding as of great value, but recommended feeding with a dropper or Breck feeder as preferable. In cases where tube feeding must be resorted to, he urged the avoidance of the nasal route because of the great danger of otitis media.

The problem of the reduction of the infant mortality rate in the United States is based very largely on the reduction of the premature births as nearly one-half of the deaths of the first year of life occur in the first month and nearly one-half of these are the result of premature birth. Our means and methods of caring for the underdeveloped baby are excellent, but the best results follow the individualization of the cases rather than the inflexible adherence to the set principles. The mortality rate may be greatly lowered by decreasing the incidence of premature births. Prenatal care of the mother is the main factor in accomplishing this. Careful handling and treatment of syphilis, tuberculosis, cardiac and renal disease, anemia and other diseases must be the rule. Another point to be emphasized is the avoidance of induction of labor until as late as possible in those cases where surgical intervention is necessary.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 18, 1936

An Instrument for Uniformly Applying Painful Stimuli of Varying Intensity (Demonstration).—MICHAEL KNIAZUK (Merck Institute of Therapeutic Research, Rahway, New Jersey). One leg of a medium-sized forceps is broken by inserting a hinge and held in position by a tensed spring. In pinching, the force exerted between the tips of the forceps depends only upon the tension of the spring, which is adjustable. After the preselected tension, which may range between 150 and 450 gm., has been reached the spring is automatically released. The compression, and thus the intensity of the stimulus, is independent of the thickness of the object between the jaws of the forceps.

Improvements in the Testing of Analgesics and Local Anesthetics (Demonstration).—HANS MOLITOR, ALBERT LATVEN, and HARRY ROBINSON (Merck Institute of Therapeutic Research, Rahway, New Jersey). *Testing of Analgesics.* The method is based on the application of graduated pressure on mice's tails and statistical evaluation of the results. Through the use of a large number of animals of the same strain for each test (at least 24 for each dose level) the influence of varying individual and strain sensitivity is minimized. The results are based on percentage of animals affected, depth of anesthesia and duration of drug action. An added advantage of the method is the requirement of only small quantities of material for a complete test, the necessary amount being at least 100 times smaller than when cats are used. For drugs of the morphin group the results are accurate within ± 13.5%.

Testing of Local Anesthetics. The application of painful stimuli of uniform, low intensity is made possible by Kniazuk's new instrument. However, normal animals respond only irregularly to such weak stimulation and it is therefore necessary to amplify the visible pain reaction. This can be done by the induction of Sherrington pseudo pain reflexes through the injection of barbiturates. Animals sensitized in such a way respond regularly. It is then easy to differentiate between effective and non-effective concentrations of local anesthetics. By keeping the stimuli just above the threshhold value, it is possible to detect and evaluate very weak or highly diluted local anesthetics.

The Anesthetic Action of Bulbocapnine.—HANS MOLITOR (Merck Institute of Therapeutic Research, Rahway, New Jersey). Bulbocapnine, tested with Eddy's tail-squeezer, acts like an analgesic of a potency of about one-fifteenth of that of morphin. If, however, the compression acting as the painful stimulus is instantaneous instead of being gradually increased, as in Eddy's instrument, practically no analgesic action is found in mice and cats. This indicates that the general analgesic effect of this drug is very weak, a result which is in agreement with clinical findings. Bulbocapnine possesses, on the other hand, a marked local anesthetic action which has not been described previously. In a frog nerve-muscle preparation a 5% solution greatly reduces and a 10% solution completely abolishes the reaction to faradic stimulation. On the rabbit's cornea complete anesthesia is produced with a 10%, marked anesthesia (in animals sensitized with Pernoston) with a 2% solution. For nerve-block anesthesia in rabbits and rats a 10% solution is effective. Complete topical anesthesia is obtained with concentrations as low as 2%. The anesthetic action is reversible in all cases. It is rather short in nerve-block anesthesia, where it rarely lasts for more than 1 hour, while the duration in topical anesthesia extends in many experiments over more than 3 hours. Controls performed with a Ringer's solution of the same pH as the bulbocapnine phosphate solution (pH 4.5) show that the anesthetic effect is caused by the drug itself.

Clinical Assays for Male Sex Hormone (Capon Comb Growth Promoting Substance) in Human Urine—Normal Individuals.—L. P. HANSEN, J. F. MCCAHEY, and D. SOLOWAY (Departments of Chemistry, Urology, and Anatomy, Jefferson Medical College). With the object of ascertaining correlations between male sex hormone elimination in the urine and various dysfunctions or abnormalities in the human, diurnal specimens of human urine were collected, preserved with chloroform, strongly acidified with hydrochloric acid and extracted with chloroform by prolonged heating on the water bath. The chloroform was separated, dried over neutral salt, and recovered by distillation. The residue was extracted with ether. The ether was removed and the residue was dispersed in olive oil, which was then used for injections into capons. Three capons were used for each test. Each capon received the extract from a 24-hour specimen of urine on each of two successive days. From measurements of the comb the maximum percentage growth was calculated.

Normal individuals of various age periods were studied with the idea of establishing a range of hormone elimination for a given period. In normal children below the age of 10 the response was found to be almost negligible. In normal young men between 20 and 30 the response varied from 21.9 to 30.5%. In composite intermittent day urine of young men of the same age period the response was considerably higher. In men of 50 and above it was definitely lower than in young men, but not invariably so. In composite urine of normal females it was found to be somewhat higher than in boys below 10, but very considerably lower than in young men. Application on the comb of the capon of the extract of urine from individual normal young men, from the extract of composite urine of normal young men, and from composite urine of normal women, produced responses varying from about 15 to 25 times the response obtained by intramuscular injections.

Clinical Assays for Male Sex Hormone in the Urine of Some Abnormal Cases.—James F. McCahey, L. P. Hansen, and D. Soloway (Departments of Urology, Chemistry, and Anatomy, Jefferson Medical College). Urinary assays for testis hormone were made in a group of individuals presenting certain abnormalities. The hormone was extracted from the urine by the acid-chloroform method. Capons were used for test animals. The results obtained as compared to values found when similar studies were carried out on normal men were as follows:

Cases of Disturbances of Spermatogenesis (Azoöspermia, Necrospermia). The testis hormone elimination was slightly lowered.

Cases of Hypopituitarism. Values obtained ranged from very low to about one-half normal findings.

Cases of Abnormal Secondary Sex Characteristics in Women. Values exceeded those found in normal men.

Arterial, Venous and Cutaneous Blood Platelet Counts in Men and Dogs Under Normal and Abnormal Conditions.—L. M. Tocantins (Department of Medicine, Jefferson Medical College). Mean values for the platelet content per c.mm. of blood, obtained from arterial, venous and cutaneous punctures in 40 normal young men: Arterial: 350,000 ± 13,889. Venous: 310,000 ± 11,937. Cutaneous: 250,000 ± 7458.

In a group of 14 normal young men examined during the winter (mean temperature 3° C.) the arterial and venous platelet counts were significantly higher than in a similar group examined during the spring (mean temperature 18.5° C.). There was no significant difference between the cutaneous blood platelet counts in these two groups. There were greater differences between the arteriovenous, arteriocutaneous and veno-cutaneous blood platelet counts in the winter than in the spring.

In naturally occurring or artificially induced thrombopenias, the initial rise in the blood platelets is detected on arterial blood and coincides with a diminution or return to normal of the mean bleeding time. Cutaneous blood platelet counts may show a thrombopenia for several days after the arterial and venous platelet counts have returned to normal. Platelet counts in arterial blood below 50,000 per c.mm. are almost always accompanied by a prolonged bleeding time.

Platelets are probably utilized as the blood goes through the capillaries. The rate and degree of this utilization will determine in a large measure the relative platelet content of cutaneous and venous blood and eventually, of arterial blood itself. If an adequate supply of platelets is not available from arterial blood (*real* thrombopenia) and a stress (trauma, etc.) is placed on the capillaries and venules, the increased utilization of platelets will result in a deficit in their number, which will be reflected in prolonged bleeding and deficient hemostasis in the affected part. In a *latent* thrombopenia the platelet count of cutaneous and sometimes that of venous blood is below 100,000 per c.mm., but that of arterial blood is often above that number, leaving, under ordinary stresses, a wider margin available for utilization, the mean bleeding time being then normal or only very slightly prolonged.

Electrical Changes in the Spinal Cord.—JOSEPH HUGHES, G. P. MCCOUCH, and W. B. STEWART (Institute of the Pennsylvania Hospital and the Department of Physiology, University of Pennsylvania). In the spinal cord, the electrical changes recorded from leads placed longitudinally on the dorsal surface of the cord excited by a single volley in a dorsal root consist of a spike followed by a longer and lower negative complex which is usually succeeded by a prolonged positive wave. The spike has been ascribed to afferent, the later components to internuncial neurons (Gasser and Graham,[1] Hughes and Gasser[2]). Whether the internuncial potentials arise solely from fibers or also from cell bodies is not known. We believe the results presented here afford a reasonable basis for conjecture. Were their origin confined to axones, the reduction of a second volley by a preceding one would be expected to affect negative and positive components in like degree. In view of the demonstration that the overwhelming majority of afferents terminate upon internuncials (Hoff[3]), cases of reflex facilitation should be accompanied by an approximately corresponding degree of increase in fiber potentials. On the other hand, if central excitatory state be associated with a negative cell potential and central inhibitory state with positivity of cells, the total electric picture might deviate from such correspondence in proportion to the changes in subliminal excitatory or inhibitory state in the cells contributing to the recorded potential.

Results. In the case of inhibition of the ipsilateral flexor reflex by a preceding volley in a contralateral root, there is a reduction in height of the negative complex approximately proportional to the reduction in the reflex response. Far different is the fate of the positive wave. Instead of a proportional reduction, the positivity is either almost or completely obliterated, even at intervals where negativity is only slightly reduced.

Reflex spacial facilitation is reflected in internuncial potentials, though by no means uniformly to a degree approximating the facilitation observed in the myographic response. Temporal facilitation has shown a five-fold increase in myographic response to the second volley with no increase whatever in the recorded cord potential.

We believe these results suggest the presence of considerable cell potentials in the electrical response of internuncial neurones.

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